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CONTENTS ЗМІСТ

Fundamental researches

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ORAL CONSUMPTION OF CAFFEINATED ENERGY DRINKS AFFECTS THE MORPHOFUNCTIONAL STATE OF STRESS-ASSOCIATED ENDOCRINE GLANDS

Tkachenko M. O., Gubina-Vakylyuk G. I., Gorbach T. V., Denysenko S. A., Tkachenko A. S., Onishchenko A. I., Zhurba E. P.
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The aim of the research was to study the features of the morphofunctional state of the pineal gland, neurohypophysis and adrenal medulla, as well as the content of serotonin and catecholamine in the blood serum of rats against the background of energy drink administration during two weeks. In animals that consumed energy drinks during two weeks at a dose of 6 ml per kg of body weight, serum serotonin and catecholamine levels were determined. Histological, including morphometric, studies of the epiphysis, posterior pituitary and adrenal medulla were performed. Against the background of energy drink administration, an increase in the content of blood serum serotonin, norepinephrine and epinephrine was detected. The morphofunctional state of the endocrine glands investigated in the present study is strongly stimulated. Indirect signs of apoptosis of parenchymal cells in the pineal gland, neurohypophysis and adrenal medulla were established. The studied stress-associated endocrine glands in animals against the background of the two-week intake of energy drinks have signs of a sharp stimulation of hormone production (serotonin, norepinephrine, epinephrine, and vasopressin).

KEY WORDS: energy drinks, neurohypophysis, pineal gland, adrenal medulla, serotonin, catecholamine

ВПЛИВ ПЕРОРАЛЬНОГО ВЖИВАННЯ ЕНЕРГЕТИЧНИХ НАПОЇВ НА МОРФОФУНКЦІОНАЛЬНИЙ СТАН СТРЕС-ОРГАНІЗУЮЧИХ ЕНДОКРИННИХ ЗАЛОЗ

Ткаченко М. О., Губіна-Вакулик Г. І., Горбач Т. В., Денисенко С. А., Ткаченко А. С., Оніщенко А. І., Журба Є. П.
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Метою роботи було вивчення особливостей морфофункціонального стану шишкоподібної залози, нейрогіпофізу і мозкової речовини надниркових залоз, а також вміст серотоніну і катехоламінів у сироватці крові щурів на тлі двотижневого вживання енергетичних напоїв. У тварин, які вживали енергетичний напій протягом двох тижнів у дозі 6 мл на кг ваги тіла, визначали вміст серотоніну і катехоламінів у сироватці крові. Проводили гістологічне, в тому числі морфометричне, дослідження епіфіза мозку, нейрогіпофізу і мозкової речовини надниркових залоз. На тлі прийому енерготоніків виявлено підвищення вмісту серотоніну, норадреналіну і адреналіну у сироватці крові. Морфофункціональний стан вивчених ендокринних залоз різко стимульований. Встановлено непрямі ознаки апоптозу паренхіматозних клітин в епіфізі мозку, нейрогіпофізі й мозковій речовині надниркових залоз. Вивчені стрес-асоційовані ендокринні залози у тварин на тлі двотижневого вживання енергетичних напоїв мають ознаки різкої стимуляції гормонопродукції (серотонін, норадреналін, адреналін, вазопресин).

КЛЮЧОВІ СЛОВА: енергетичні напої, нейрогіпофіз, епіфіз, мозкова речовина надниркових, серотонін, катехоламіни

ВЛИЯНИЕ ПЕРОРАЛЬНОГО УПОТРЕБЛЕНИЯ ЭНЕРГЕТИЧЕСКИХ НАПИТКОВ НА МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ СТРЕСС-ОРГАНИЗИРУЮЩИХ ЭНДОКРИННЫХ ЖЕЛЕЗ

Ткаченко М. А., Губина-Вакулик Г. И., Горбач Т. В., Денисенко С. А., Ткаченко А. С., Онищенко А. И., Журба Е. П.
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Целью работы явилось изучение особенностей морфофункционального состояния шишковидной железы, нейрогипофиза и мозгового вещества надпочечников, а также содержание серотонина и катехоламинов в сыворотке крови крыс на фоне двухнедельного употребления энергетических напитков. У животных, которые употребляли энергетический напиток в течение двух недель в дозировке 6 мл на кг веса, определяли содержание серотонина и катехоламинов в сыворотке крови. Проводили гистологическое, в том числе морфометрическое, исследования эпифиза мозга, нейрогипофиза и мозгового вещества надпочечников. На фоне приема энерготоников обнаружено повышение содержания серотонина, норадреналина и адреналина в сыворотке крови. Морфофункциональное состояние изученных эндокринных желез резко стимулировано. Установлены косвенные признаки апоптоза паренхиматозных клеток в эпифизе мозга, нейрогипофизе и мозговом веществе надпочечников. Изученные стресс-ассоциированные эндокринные железы у животных на фоне двухнедельного употребления энергетических напитков имеют признаки резкой стимуляции гормонопродукции (серотонин, норадреналин, адреналин, вазопрессин).

КЛЮЧЕВЫЕ СЛОВА: энергетические напитки, нейрогипофиз, эпифиз, мозговое вещество надпочечников, серотонин, катехоламины

INTRODUCTION

Since the appearance of caffeinated energy drinks in Europe in 1987, they have been gaining popularity on the market all over the world [1]. They are used primarily by youth to improve mental and physical performance and endurance. One of the active substances present in such drinks is caffeine. According to Food and Drug Administration, the daily intake of caffeine should be limited to 300 mg. However, the content of caffeine per one can or a small bottle of energy drinks may reach 550 mg [2]. Apart from caffeine, caffeinated beverages contain other methylxanthines, glucurono-lactone, guarana, group B vitamins, taurine, ginseng, etc. In addition, caffeinated energy drinks have a lot of sucrose [1]. It has been reported that the intake of caffeine-containing energy drinks has been associated with health-related problems among their consumers. In particular, it has been demonstrated that the consumption of caffeinated energy drinks and their ingredients affects mood and the state of the nervous system, contributes to the development of cardiovascular disorders, causes changes in the gastrointestinal tract and leads to significant metabolic effects [1–4]. Despite numerous reports about negative effects of caffeinated energy drinks on the metabolism, the cells of such beverages are growing and the energy drink market size reaches over forty billion dollars.

Taking into account the fact that caffeine-containing beverages affect mood, sleeping and their consumption may result in the development of neurological and psychological effects [2], it is of huge importance to find out how their intake affects the state of stress-associated endocrine glands [5].

OBJECTIVE

The aim of the research was to study the features of the morphofunctional state of the pineal gland, neurohypophysis and adrenal medulla, as well as the content of serotonin and catecholamine in the blood serum of rats against the background of energy drink administration during two weeks.

MATERIALS AND METHODS

According to the experiment, twenty WAG adult rats were randomly divided into two groups: experimental (n = 10) and control (n = 10). Rats from the experimental group were orally administered caffeine-containing energy drink of the famous brand once per day at a dose of 6 ml per 1 kg of weight during two weeks. The control group consisted of healthy intact animals.

The European Convection for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes and Directive 2010/63/EU on the protection of animals used for scientific purposes adopted on September 22, 2010 were strictly followed when carrying out our research. The research design was approved by the Committee of Bioethics (Kharkiv National Medical University).

Animals from both groups were killed by decapitation. The pineal, pituitary and adrenal glands were isolated and fixed in 10 % neutral formalin and embedded in paraffin. Micro-sections were stained using hematoxylin-eosin and Einarsson gallocyanin chrome alum. In addition to the general description of histological features, a morphometric study was

performed to determine the area of the nuclei (karyometry) of neuroendocrinocytes in adrenal medulla, pinealocytes, and pituitocytes. The amount of pinealocytes in a limited area of the microslide (S = 500 μm^2) was calculated.

Immediately after decapitation, blood was collected in order to obtain serum. The content of catecholamine and serotonin in blood serum was determined using the spectrofluorometric method [6].

«GraphPad Prism 5» was used to statistically process the obtained data. To evaluate the quantitative differences between experi-mental and control groups, the nonparametric Mann-Whitney U test was chosen. The results were statistically significant at $p < 0.05$.

RESULTS AND DISCUSSIONS

The tissue of the pineal gland in control animals looks compact with insignificant small voids. Thus, its structure can be considered cellular with signs of the formation of the lobular structure. It is worth noting that many pinealocytes have a large light (euchromic) nucleus with a clearly visible nucleolus. In the pinealogy, such pinealocytes are considered to be peptide-producing. Pinealocytes with darker and angular nuclei are believed to produce indolamines: serotonin and melatonin. It is interesting to note that peptide-producing pinealocytes have eosinophilic cytosol, whereas cytosol in indolamine-generating cells looks vacuolated. Obviously, if pinealocytes simultaneously produce both polypeptides and indolamines, their cytosol seems to be granular or foamy. Such pinealocytes prevail in animals from the control group. Some small-sized «empty» areas can be found in the pineal tissue. They are formed as a result of apoptotic cell death of 1–2–3 pinealocytes (Fig. 1).

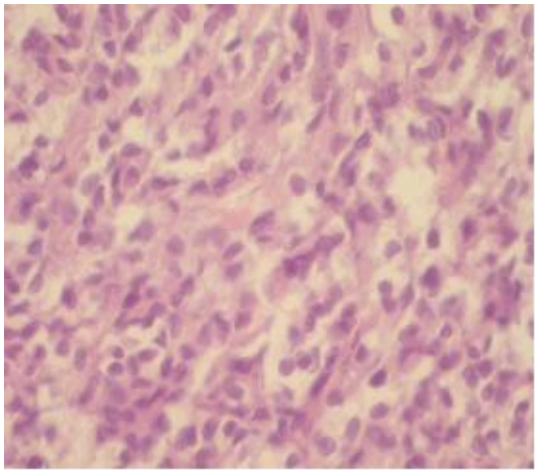

Fig. 1. Pineal tissue of an animal from the control group is compact and cellular. The huge number of pinealocytes with granular cytosol is observed. Hemotoxylin and eosin staining, x400.

In the experimental group, the histological structure of the pineal gland is characterized by the noticeable shift towards the lobular structure. Larger «empty» foci are observed. At their edges isolated pinealocytes are located. Such changes indicate a massive (several pinelaocytes at once) death of pinealocytes by apoptosis. Detailed analysis of the cytological features of pinealocytes allows us to presume that pinealocytes with morphofunctional features of indolamine-producing cells prevail in the experimental group (Fig. 2).

The morphometric study revealed a significant reduction in the amount of pinaleocytes per a fixed area of microslides (S = 500 μm^2) in the experimental group compared to the control group: 5.1 ± 0.3 and 7.7 ± 0.4 ($p < 0.001$), respectively. In addition, karyometry showed that nuclei of pinealocytes in the epiphysis in animals from the experimental group are significantly larger than in the control group: 19.23 ± 0.36 μm^2 and 14.35 ± 0.34 μm^2 ($p < 0.001$), respectively. This indicates that pinealocytes have functioned strenuously producing more indolamines.

Compared to the control group, there is an abundant capillary network in the neurohypophysis of animals from the experimental group (Fig. 3, 4). It is well visualized on microslides stained by Mallory. There are clusters of Herring bodies that adsorb alcian blue well along the capillaries, surrounding them (Fig. 4).

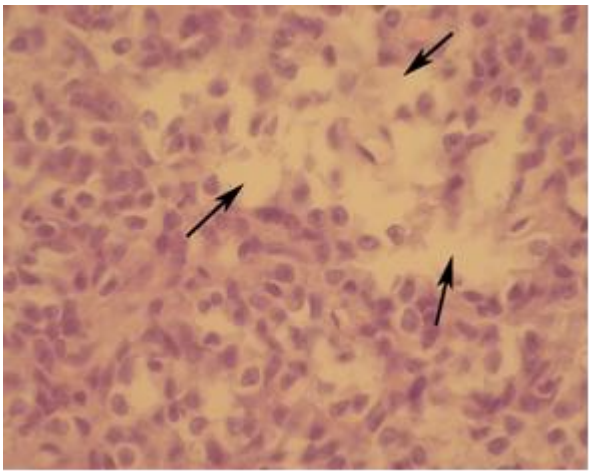

Fig. 2. Pineal tissue of an animal from the experimental group. Empty areas (marked with arrows) with separate pinealocytes are observed. Such changes are probably the result of pinealocyte apoptosis. The total number of pinealocytes is reduced. Hematoxylin and eosin staining, x400.

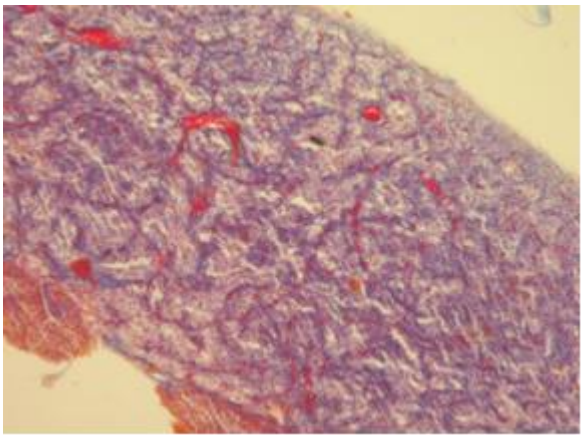

Fig. 3. Posterior pituitary of an animal from the control group. The capillary network is moderate. Along the vessels there are alcian blue-positive formations with spherical Herring bodies. Mallory's staining, x100.

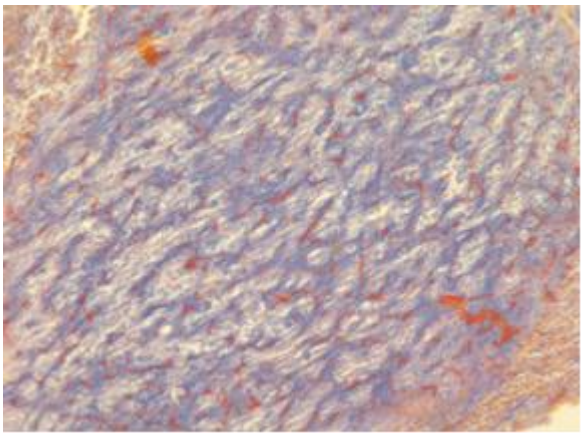

Fig. 4. Posterior pituitary of an animal from the experimental group is characterized by the more pronounced capillary network, higher volume of Herring bodies with the decreased optical density of the substrate. Mallory's staining, x100.

The accumulation of vasopressin is much more noticeable in the experimental group in comparison with the control group. Pituicytes, which are elements of macroglia and perform trophic and supporting functions, are hyperplastic. Their size is increased: 22.60 ± 0.04 μm^2 in the control group against 23.91 ± 0.05 μm^2 in the experimental group ($p < 0.001$). The presence of microglia is noticeable, which can be explained by more active apoptotic processes and the need to utilize apoptotic bodies in the neurohypophysis in the experimental group.

Thus, microscopic signs of an increase in the morphofunctional activity of the posterior pituitary gland in animals receiving caffeinated energy drinks at a dose of 6 ml per 1 kg of body weight were found. Such conclusion is confirmed by a more developed capillary network, the increased accumulation of the substrate in the enlarged Herring bodies, as well as by hyperplasia and hypertrophy of the pituitocytes.

The study of adrenal medulla in animals from the experimental group showed that the cells had a more eosinophilic cytosol with some visible vacuoles. Along with small, dark nuclei there are areas filled with large, light nuclei that sometimes have two nucleoli, which points to polyploidy. A considerable increase in the size of the neuroendocrinocyte nuclei in the experimental group was found. It was 13.6 ± 0.4 μm^2 in the control group and reached 15.3 ± 0.5 μm^2 in the experimental one ($p < 0.01$), which might indicate an increased synthesis and secretion of catecholamine. Some small cellular debris, probably apoptotic bodies, can be seen occasionally. They indicate the increased load and cell death rate, which is confirmed by the increased morphofunctional load of adrenal neuroendocrinocytes.

Such significant increase in the levels of stress-related hormones and serotonin against the background of the increased morphofunctional activity of pinealocytes (overproduction of indolamines), adrenal and posterior pituitary neuroendocrinocytes leads to the exertion of all regulatory systems, behavioral responses due to compensatory abilities of the body, and creates a high risk of pathological processes. Signs of apoptosis in the pineal gland («empty» areas in the pineal tissue), adrenal medulla (apoptotic bodies) and posterior pituitary gland (tissue is rich in macroglia) indicate the development of atrophization.

Table 1

The content of serotonin and catecholamine in blood serum of animals against the background of caffeinated energy drink administration (Me [25 %; 75 %])

Groups	Serotonin, nmol/l	Norepinephrine, nmol/l	Epinephrine, nmol/l
Control group (n = 10)	203,9 [197,1; 209,7]	12,44 [12,06; 12,84]	0,86 [0,82; 0,88]
Experimental group (n = 10)	596,2 [578,7; 612,7] p < 0,0001	24,34 [22,76; 25,10 p < 0,0001	2,62 [2,30; 2,94] p < 0,001

Notes: 1. n is the number of animals in the group; 2. p is a significance compared to the control group

CONCLUSIONS

1. Oral consumption of energy drinks during two weeks by experimental animals led to morphological changes in the pineal gland (prevalence of indolamine-producing pinealocytes), an increased load on these cells and probably their faster and frequent apoptosis. The number of pinealocytes in the pineal gland decreases and their morphofunctional load increases.

2. Short-term administration (14 days) of caffeinated energy drinks affects the morphofunctional state of posterior pituitary, which can be highly likely interpreted as a result of overproduction of vasopressin.

3. Overproduction of serotonin by pynealocytes and catecholamine by adrenal glands is confirmed by their higher levels in blood serum of animals after the two-week-long intake of energy drinks compared to the control group.

PROSPECTS FOR FUTURE STUDIES

It is promising to study effects of caffeinated energy drinks on the morphofunctional state of other brain structures and features of neurotransmitter metabolism in them.

REFERENCES

1. Energy drink consumption: beneficial and adverse health effects / [A. A. Alumni] // International Journal of Health Sciences. – 2015. – Vol. 9 (4). – P. 468–474.
2. A review of energy drinks and mental health, with a focus on stress, anxiety, and depression / [G. Richards, A. P. Smith] // Journal of Caffeine Research. – 2016. – Vol. 6 (2). – P. 49–63. doi:10.1089/jcr.2015.0033
3. Energy drinks: Potions of illusion / [N. Bedi, P. Dewan, P. Gupta] // Indian pediatrics. – 2014. – Vol. 51 (7). – P. 529–533.
4. Review of published cases of adverse cardiovascular events after ingestion of energy drinks. / [M. Goldfarb, C. Tellier, G. Thanassoulis] // The American journal of cardiology. – 2014. – Vol. 113 (1). – P. 168–172.
5. Meerson FZ, Pshennikova MG. Adaptacija k stressornym situacijam i fizicheskim nagruzkam. M., Medicina, 1988. – 258 p.
6. The neuropharmacology of taurine / [A. Barbeau, N. Inoue, I. Tsukada, R. F. Butterworth] // Life Sci. – 1975. – Vol. 17. – P. 669–678.

Clinical researches

UDC 616.379-008.64

COEXISTANCE OF DIABETES MELLITUS AND THYROID DISORDERS: A VIEW ON DYSFUNCTION OF THE ENDOCRINE SYSTEM

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Thyroid disorders in patients with diabetes mellitus were studied in 196 patients, divided into 4 main groups (hyperthyroidism in patients with diabetes, hypothyroidism in patients with diabetes, euthyroidism in patients with diabetes and diabetes patients without any thyroid pathology). It was found that diabetes and thyroid disorders have been shown mutually influence on each other and proved associations between both conditions. Compensation of thyroid function due to adequate therapy leads to controlled hyperglycemia, positive arterial hypertension disease mode and better diabetes mellitus outcome.

KEY WORDS: Diabetes Mellitus, thyroid dysfunction, comorbidities, arterial hypertension, complications

СПІВІСНУВАННЯ ЦУКРОВОГО ДІАБЕТУ І ЗАХВОРЮВАННЬ ЩИТОВИДНОЇ ЗАЛОЗИ: ПОГЛЯД НА ДИСФУНКЦІЮ ЕНДОКРИНОЇ СИСТЕМИ

Аду Альберт Асаре[1], Даниель К. Сем[2], Адейемі Адедайо М.[1], Махаринська О. С.[1]
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Були вивчені особливості впливу порушень щитовидної залози у хворих на цукровий діабет у 196 пацієнтів, які були розділені на 4 основні групи (гіпертиреоз у хворих на цукровий діабет, гіпотиреоз у пацієнтів із цукровим діабетом, еутиреоз у пацієнтів із цукровим діабетом та пацієнти з діабетом без будь-якої патології щитовидної залози). Було встановлено, що цукровий діабет і розлади щитовидної залози взаємно впливають один на одного і підтверджено асоціацію між обома захворюваннями. Компенсація функції щитовидної залози за рахунок адекватної терапії призводить до контрольованої гіперглікемії, полегшеної течії артеріальної гіпертензії у таких хворих і зниження кількості негативних наслідків захворювання.

КЛЮЧОВІ СЛОВА: цукровий діабет, дисфункція щитовидної залози, супутні захворювання, артеріальна гіпертензія, ускладнення

СОСУЩЕСТВОВАНИЕ САХАРНОГО ДИАБЕТА И РАССТРОЙСТВ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ВЗГЛЯД НА ДИСФУНКЦИЮ ЭНДОКРИННОЙ СИСТЕМЫ

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Были изучены особенности влияния заболеваний щитовидной железы на пациентов с сахарным диабетом у 196 пациентов, разделенных на 4 основные группы (гипертиреоз у пациентов с диабетом, гипотиреоз у пациентов с диабетом, эутиреоз у пациентов с диабетом и больные с сахарным диабетом без какой-либо патологии щитовидной железы). Было показано, что диабет и заболевания щитовидной железы взаимно влияют друг на друга и подтверждена ассоциация между обоими состояниями. Компенсация функции щитовидной железы вследствие адекватной терапии приводит к контролируемой гипергликемии, более легкому течению артериальной гипертензии и уменьшению частоты тяжелых исходов заболевания.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет, дисфункция щитовидной железы, сопутствующие заболевания, артериальная гипертензия, осложнения

INTRODUCTION

Diabetes mellitus (DM) and thyroid dysfunction are two the most common endocrine disorders diagnosed and found in different ages and subgroups of patients worldwide. Both of them influence clinical course of each other. The total prevalence of DM is increasing day by day and World Health Organization is declared DM rate about 366 millions in 2030 in the world, affecting 4,4 % of all age groups [1]. Thyroid disorders can have a major impact on glucose control, and untreated thyroid disorders affect the management and clinical course of diabetes in patients.The frequency of thyroid dysfunction in diabetic patients is higher than in the general population: according to the American Diabetes Association's 2016 Standards of Medical Care in Diabetes autoimmune thyroid disease occurs in 17 to 30 percent of people with DM type 1. A recent studies data in 10 920 patients with DM showed that a mean frequency of thyroid disease is around 11 % [2]. The pathophysiological basis of this association rests on a complex interaction of common signaling pathways and, in the case of type 1 diabetes and autoimmune thyroid disease [1], as result of the impact of particular environmental factors on individuals with genetical susceptiblity, which leads to loss of self-tolerance and there by triggering disease or a linked genetic susceptibility for both thyroid disease and DM [3].

OBJECTIVE

The aim of the current study was to investigate the influence of thyroid gland dysfunction on patients with diabetes mellitus. Can present interactions between two endocrine diseases lead to increasing of the severity of the patient's health state and loss of hyperglycemia effective control?

MATERIALS AND METHODS

In our retrospective study were included 196 patients (65 men, 33 % and 134 women, 68 %) diagnosed with diabetes mellitus, treated in 13 Kharkiv city hospital, Ukraine, with or without thyroid disorders (36 patients with hypothyroidism, 6 patients with hyperthyroidism, 51 patient with euthyroidism and 106 patients with diabetes mellitus itself). All diagnoses were maiden and confirmed by 13 Kharkiv city hospital endocrinologist previously according to criterias of the main treatment protocols of the Health Ministry of Ukraine and WHO [4]. Patients were divided into 4 study groups: (1) DM in patients with hypofunction of thyroid gland (mean age 62 ± 2 years, 2 patients with DM 1 and 34 patients with DM 2 type); (2) diabetes in patients with hyperfunction of thyroid gland (mean age 71 ± 3 years, 0 patients with DM 1 and 6 patients with DM 2 type); (3) diabetes in patients with compensated function of thyroid gland (mean age 62 ± 2 years, 3 patients with DM 1 and 48 patients with DM 2 type) and (4) diabetes mellitus patients without dysfunction of thyroid gland (mean age 63 ± 1 years, 9 patients with DM 1 and 97 patients with DM 2 type). All groups were equal by gender, age, duration of DM and quantity of patients with diagnosis DM 1type and 2type inside of each group (see table 1). These parameters were analysed: levels of fasting blood glucose, HbA1c, creatinine, blood pressure, incidence of the main diabetes complications in all groups, appearance and severity of Arterial Hypertension (AH). Exclusion criterias were: patients with neoplasia and paraneoplastic syndrome, diffuse diseases of connective tissues, cardiomyopathy of any genesis, tuberculosis or other opportunistic infections, alcoholics or drug addicted patients, psychiatric disorders. Duration of DM was equal in all groups (7 ± 1 (1) vs 7 ± 3 (2) vs 8 ± 1 (3) vs 7 ± 1 (4) years relatively). Diagnosis Arterial Hypertension was present in 189 patients in the study (96 %) and all of them received antihypertensive treatment according to national guidelines and hypertension degree with 5 main antihypertensive drug classes. Diagnosis AH stage 1 was maden in 99 patient's cases (50 % of patients in the study, 14(1) vs 1(2) vs 27(3) vs 57(4) respectively), AH stage 2 in 11 patients in the study (6 % of patients in the study, 2(1) vs 0(2) vs 3(3) vs 6(4) respectively), AH stage 3 in 33 patients in the study (17 % of patients in the study, 10 (1) vs 6(2) vs 2(3) vs 15(4) respectively), see table 1.

Table 1

Study groups description (data has been presented as absolute count (percentage); age, systolic and diastolic pressures and duration of DM are represented as mean ± standard error of mean)

Demographic Variables		DM + Hypothyroidism 1 group (36 patients)	DM + Hyperthyroidism 2 group (6 patients)	DM + Euthyroidism 3 group (51 patients)	DM 4 group (106 patients)	P-value
Sex	Male	15 (42 %)	1 (17 %)	13 (25 %)	36 (34 %)	0.348
	Female	21 (58 %)	5 (83 %)	38 (75 %)	70 (66 %)	
Age		62 ± 2	71 ± 3	62 ± 2	63 ± 1	0.336
DM types	Type 1	2 (6 %)	0 (0.0)	3 (6 %)	9 (9 %)	0.796
	Type 2	34 (94 %)	6 (100 %)	48 (94 %)	97 (91 %)	
SAP		161 ± 6	148 ± 2	142 ± 2	146 ± 2	< 0.05
DAP		97 ± 4	83 ± 5	80 ± 1	86 ± 1	< 0.0001
Duration of DM (years)		7 ± 1	7 ± 3	8 ± 1	7 ± 1	0.836
Hypertension groups	Normal BP	0 (0.0)	0 (0.0)	1 (2 %)	6 (6 %)	2- 1,3,4 -< 0.05 1-4– 0.02 1-3 – 0.001
	Pre-hypertension	10 (27 %)	0 (0.0)	18 (35 %)	22 (20 %)	
	Stage 1	14 (39 %)	1 (17 %)	27 (53 %)	57 (54 %)	
	Stage 2	2 (5 %)	0 (0.0)	3 (6 %)	6 (6 %)	
	Stage 3	10 (29 %)	6 (83 %)	2 (4 %)	15 (14 %)	

The data is entered into Microsoft Excel database 2010. Statistic evaluation of the results was performed in Statistica program by parametric methods to estimate the mean (M) and standard error of mean and non-parametric Student's T-test. Study limitations: small groups of patients with thyroid disorders in combination with DM.

RESULTS AND DISCUSSION

Despite the fact that all groups were equal by the main parameters list, we noticed that the prevalence of combined DM – thyroid pathology in female patients was higher in each group (1–3 groups in our study). In scientific medical sources indicated that usual prevalence of DM-thyroid pathology combination is in two fold higher in woman subgroup that in men, which is corresponds to results in our study [2]. Levels of BP, both systolic and diastolic, in patients with hypothyroidism group (1), despite antihypertensive treatment prescribed for all patients, were statistically higher than in other groups. It can be explained by the fact that in patients with Hypothyroidism T3 hormone deficiency leads to peripheral vasoconstriction with increased arterial stiffness, which is an important determinant of arteriosclerosis and changes in arterial wall elasticity [5]. Also increasing of systolic and diastolic BP may stimulate changes inside of the arterial wall with further reducing of elasticity and increasing of the wall stiffness. In this group of patients (1) and also in patients with combination of Hyperthyroidism and DM (2group) quantity of patients with 3rd stage of Arterial Hypertension by WHO classification with the highest prevalence of AH complications were higher than in uncompromised function of thyroid gland groups (3, 4). This possibly can be explained by the main effects of thyroid hormones as increased β-adrenergic activity with heart rate and cardiac contractility increasing, increasing

of systolic and mean pulmonary artery pressures, cardiac output, diastolic relaxation, appearance of atrial arrhythmias and myocardial oxygen consumption. Also increased density of β-adrenergic receptors in the renal cortex usually results in increased plasma renin, angiotensin II, and serum angiotensin converting enzyme levels especially in DM patients with compromised function of kidneys, micro and macrovascular DM complications present [6].

Incidence of the main DM complications as stroke, myocardial infarction (MI), diabetic nephropathy (DN) and chronic heart failure (CHF) were investigated in our study. So stroke incidence were significantly higher in DM +Hyperthyroidism group (1) comparing with Hypothyroidism group patients (2), but there were no significant difference between (2) group and groups with uncompromised thyroid function despite prevalence of stroke incidence in 2nd group (83 % (2) vs 2 %(3) vs 3 % (4) respectively) (see table 2). Hyperthyroidism as well-known disorder associated with an increased risk of atrial fibrillation (AF) especially among 60 years or older patients and due to AF also with the high risk for cardioembolic events as a cause of stroke [7] in presence of compromised endothelial function, dyslipidemia, insulin resistance, microvasculopathy in DM patients may lead to increased incidence of stroke events especially ischemic one in patients with DM comparing with other groups.

Table 2

Levels of DM complications in study groups

Complications	1group (patients, %)	2 group (patients, %)	3 group (patients, %)	4 group (patients, %)	p
Stroke	2 (5 %)	5 (83 %)	1 (2 %)	3 (3 %)	1–2 groups – 0,0001
MI	2 (5 %)	0 (0.0)	2 (4 %)	2 (1.8 %)	> 0.05
Diabetic nephropathy	21 (58 %)	6 (100 %)	20 (39 %)	60 (57 %)	1–2 groups – 0,03 2–4 groups – 0,02
CHF	29 (80 %)	6 (100 %)	36 (70 %)	66 (62 %)	1–4 groups – 0,04 1–2 groups – 0,001 2–4 groups – 0,01 2–3 groups – 0,005

No significant difference was found in study groups in incidence of MI, which can be explained by small quantity of patients with thyroid pathology presented in the study. But if we talk about diabetic nephropathy, were found statistically significant prevalence of DN in hyperthyroidism group (2) patients comparing with hypothyroidism group (1) and patients with DM without thyroid pathology (4). Incidence of DN was higher in 2nd group too, comparing with euthyroidism group (3), but difference was not significantly higher (100 % vs 39 % respectively). Diabetic nephropathy is one of the most common microvascular complications of diabetes mellitus and several clinical studies show that thyroid dysfunction is related to renal disease, especially hypothyroidism. Thyroid dysfunction causes remarkable changes in renal blood flow, glomerular filtration rate, tubular secretory and absorptive capacity, electrolyte pumps, and kidney structure [8]. Recent studies suggest that hyperthyroidism results in increased filtration pressure because of intra-glomerular hypertension and hyperfiltration. Also it may lead to proteinuria appearance, one of the main factors of direct renal injury and hyperthyroidism-induced increased mitochondrial energy metabolism along with down-regulation of superoxide dismutase contributes to the increased free radical generation and consequent renal injury too [9]. But also this

result can be explained by limitation of our study – only a few patients in 2nd group. This fact despite equality of all groups by main parameters may influence the result.

Moreover, thyroid dysfunction can be counted as risk factor of CHF appearance. Untreated hyperthyroidism as hypothyroidism too has been reported as a common cause of CHF. Persistent subclinical thyroid dysfunction has recently been associated with the development of CHF in patients with and without underlying heart disease [6]. In our study CHF incidence were significantly higher in hyperthyroidism group (2) comparing with other 3 groups (100 % (2) vs 80 % (1) vs 70 % (3) vs 62 % (4) respectively). Otherwise, prevalence of CHF episodes in hypothyroidism group (1) was significantly higher too comparing with DM group without thyroid diseases present (4) (see table 2). In multiple studies has been demonstrated that the heart is particularly vulnerable to the reduction in local T_3 levels which is essential to preserve both cardiac morphology and performance in adult life [6]. Thyroid hormones also increase cardiac output by affecting stroke volume and hear rate, several important cardiac structural and functional proteins are transcriptionally regulated by T_3, thyroid hormone regulates the transcription of pacemaker-related genes and hyperpolarization-activated cyclic nucleotide-gated channels 3 and 4 and guanine nucleotide regulatory proteins. Furthermore, hyperthyroiddism is characterized by a high cardiac output state with a remarkable increase in heart rate and cardiac preload and a reduction in peripheral vascular resistance, resulting in a hyperdynamic circulation and increased risk of atrial arrhythmias and cardiac death [10]. Other studies proved that due to decreased αMHC expression and increased βMHC expression hypothyroidism causes cardiacatrophy and may lead to chamber dilatation and impaired myocardial blood flow [11]. All these factors make the heart vulnerable in case of thyroid disorders present especially in DM patients with high incidence of atherosclerosis and arterial hypertension, presence of microvasculopathy and DN.

Optimal hyperglycemia control is the key-task in treatment of DM that helps to avoid the appearance of the main complication of DM, make lesser severity of disease, reduce mortality and improve prognosis for the patient's life. In our study we found that fasting blood glucose levels were markedly raised in both thyroid disorders (10.18 ± 0.72 mmol/l in (1) and 16.25 ± 3.07 mmol/l in (2) vs 9.07 ± 0.35 mmol/l in (3) and 9.21 ± 0.39 mmol/l in (4)), but significantly higher these levels were only if comparing (2) group level with (3) and (4) groups of patients with uncompromised function of thyroid gland (p-0.02). Similar situation was in comparing of HbA1c group levels as marker of hyperglycemia control during last 3 month. We found that HbA1c levels were markedly raised in both thyroid disorders (7.73 ± 0.29 % in (1) and 7.48 ± 0.81 % in (2) group vs 6.89 ± 0.17 %in (3) and 6.95 ± 0.11 % in (4)), but significantly higher these levels were only if comparing (1) hypothyroidism group level with (3) and (4) groups of patients with uncompromised function of thyroid gland (p-0.01). Non-optimal hyperglycemia control in this patient's group and could be explained by increased insulin resistance, due to reduced rate of insulin degradation in hypothyroidism which may lower the exogenous insulin requirement. Otherwise, uncontrolled hyperglycemia may lead to an impairment in peripheral conversion of T4 to T3, reducing of T3 levels and worsening of hypothyroidism outcome with enlarged dosages of replacement therapy needed. Studies done in hypothyroid patients showed elevated HbA1c not only in the presence of diabetes but also in non-diabetic subjects. Whereas, both clinical and subclinical hypothyroidisms have been recognized as insulin resistant states [12]. In hyperthyroidism patients, the hyperglycemia may improve with treatment of thyrotoxicosis. Otherwise, underlying hyperthyroidism should be considered in diabetic patients with unexplained worsening hyperglycemia due to the increase in glucose gut absorption mediated by the excess thyroid hormones, the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors, increased lipolysis. Restoration of euthyroidism will lower blood glucose level [13]. In our study we also found existence of middle-strength positive (0,5) correlation between HbA1c level and creatinine levels in group of DM+Hyperthyroidism (2) patients with (higher level of HbA1c is – higher level of creatinine will be), which proves strong interactions between both endocrine disorders. From one hand, the kidneys play a role in glucose

homeostasis, in patients with DM decreased renal gluconeogenesis, microvascular changes, decreased insulin clearance, and inflammation-induce insulin resistance is a base of renal injury in patients with DM [14]. From other hand, hyperthyroidism is a risk factor of kidney injury with kidney function impairment and further glucose homeostasis worsening despite treatment prescribed.

CONCLUSIONS

1. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported. Compensation of thyroid function due to adequate therapy leads to controlled hyperglycemia, less frequency of DM and better DM outcome

2. Hyperthyroidism as hypothyroidism impairs glycemic control in diabetic subjects, but hypothyroidism patients alter carbohydrate metabolism with inability to gain stable compensation of DM compering with euthyroidism and DM without thyroid dysfunction.

3. Despite increased levels of BP, both systolic and diastolic, in patients with hypothyroidism group, prevalence of AH 3rd stage and AH complications were significantly higher in hyperthyroidism which requires more strict control of blood pressure levels and AH treatment in this group of patients.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate and important to study influence of DM course on thyroid function control and possible interactions between medication using in treatment of both disorders in the aim of improvement of diseases course, decreasing of complications and increasing of survival rate.

REFERENCES

1. Huber A. Joint genetic susceptibility to type 1 diabetes and autoimmune thyroiditis: from epidemiology to mechanisms. / A. Huber, F. Menconi, S. Corathers [et al.] // Endocrine Reviews. –2008. – No. 29. – p. 697–725.
2. Kadiyala, R. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. / R. Kadiyala, R. Peter, O. E. Okosieme, // International Journal of Clinical Practice. – 2010. – No. 64. – p. 1130–1139.
3. Duntas L. H. The interface between thyroid and diabetes mellitus/ L. H. Duntas, J. Orgiazzi, G. Brabant // Clinical endocrinology. – 2011. – vol. 75 (1). – p. 1–9.
4. Unificovaniiclinichnii protocol pervinnoi, extrennoi, vtorinnoi (specializovanoi) ta tretinnoi (visokospecializovanoi) medichnoidopomogi (UKPMD) «Cukroviidiabet 1 tipuumolodihludei ta doroslich», 2014, MOZ, Ukraine.
5. Hage M. Thyroid Disorders and Diabetes Mellitus / M. Hage, M. S. Zantout, S. T. Azar // Journal of Thyroid Research. – Volume 2011, http://dx.doi.org/10.4061/2011/439463
6. Biondi B. Mechanisms in endocrinology: Heart failure and thyroid dysfunction / B. Biondi // Eur J Endocrinol. – 2012. – No. 167. – p. 609–618.
7. Sheu J. J. Hyperthyroidism and Risk of Ischemic Stroke in Young Adults. A 5-Year Follow-Up Study / Jau-Jiuan Sheu, Jiunn-Horng Kang, H. C. Lin, et al. // Stroke. – 2010. – No. 41. – p. 961–966.
8. Wu J. Free Triiodothyronine Levels Are Associated with Diabetic Nephropathy in Euthyroid Patients with Type 2 Diabetes / J. Wu, LiX., Y. Tao, Y. Wang, Y. Peng // International Journal of Endocrinology. – 2015, http://dx.doi.org/10.1155/2015/204893
9. Vargas F. Vascular and renal function in experimental thyroid disorders. / F. Vargas, J. M. Moreno, I. Rodríguez-Gómez [et al.]. // Eur J Endocrinol. – 2006. – No. 154 (2). – p. 197–212.
10. Biondi B. How could we improve the increased cardiovascular mortality in patients with overt and subclinical hyperthyroidism? / B. Biondi // European Journal of Endocrinology. – 2012. – No. 167. – p. 295–299.
11. Gerdes A. M. Thyroid replacement therapy and heart failure. / A. M. Gerdes, G. Iervasi // Circulation. – 2010. – No. 122. – p. 385–393.
12. Kim M. K. Effects of thyroid hormone on A1C and glycated albumin levels in non-diabetic subjects with overt hypothyroidism. / M. K. Kim, H. S. Kwon, K. H. Baek [et al.]. // Diabetes Care. – 2010. – No. 33 (12). – p. 2546–8.
13. Potenza M. Excess thyroid hormone and carbohydrate metabolism. / M. Potenza, M. A. Via, R. T. Yanagisawa // Endocrine Practice. – 2009. – No. 15. – p. 254–262.
14. Pecoits-Filho R. Interactions between kidney disease and diabetes: dangerous liaisons / R. Pecoits-Filho, H. Abensur, C. C. R. Betônico [et al.]. // Diabetol Metab Syndr. – 2016. – No. 8. – p.50.

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INFLUENCE OF THE TOTAL POWER OF THE HEART RATE VARIABILITY SPECTRUM ON THE SPECTRAL PARAMETERS DISTRIBUTION IN PATIENTS WITH ARTERIAL HYPERTENSION IN A PACED BREATHING TEST

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To determine the effect of the total power (TP) of the heart rate variability (HRV) spectrum on the distribution of high, low and very low frequency waves, 40 patients with arterial hypertension (AH) at the age of 58 ± 9 years were divided into 5 groups according to the degree of TP decrease in the initial stage of the test: 1st – more than 3000 ms^2; 2nd – 3000–2000 ms^2; 3rd – 2000-1000 ms^2; 4th – 1000–500 ms^2; 5th – less than 500 ms^2. To assess HRV parameters in each group, 3 stages of the paced breathing test with a double (light and sound) metronome were evaluated; the hardware and software complex «Cardiolab» («HAI-Medica») was used. The distribution of the parameters was estimated taking into account the median, 25 and 75 quartiles. To estimate the differences between the statistical samples, the nonparametric Mann-Whitney U-test was used, as well as the *Craskell–Wallis* criterion. Statistically significant differences were considered between the data at a value of $p < 0.05$. It was found that the greater is the degree of TP reduction, the more significant is the autonomic imbalance, as well as the decrease in the influence of paced breathing on the regulation of the heart rhythm; at TP values below 1000 ms^2 not only the parasympathetic component decrease is observed, but also the transition from sympathicotonia to the neurohumoral factors prevalence.

KEY WORDS: arterial hypertension, heart rate variability, paced breathing

ВПЛИВ ЗАГАЛЬНОЇ ПОТУЖНОСТІ СПЕКТРУ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ НА РОЗПОДІЛ СПЕКТРАЛЬНИХ ПОКАЗНИКІВ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ В ПРОБІ З МЕТРОНОМІЗОВАНИМ ДИХАННЯМ

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Для визначення впливу загальної потужності (ТР) спектра варіабельності серцевого ритму (ВСР) на розподіл хвиль високої, низької і дуже низької частоти 40 пацієнтів з артеріальною гіпертензією (АГ) у віці 58 ± 9 років були розділені на 5 груп за ступенями зниження ТР на фоновому етапі проби: 1а – більше 3000 $мс^2$; 2а – 3000–2000 $мс^2$; 3тя – 2000–1000 $мс^2$; 4а – 1000–500 $мс^2$; 5а – менше 500 $мс^2$. Для оцінки показників ВСР в кожній групі оцінювалися 3 етапи проби з метрономізованим диханням з подвійним (світловим і звуковим) метрономом; використовувався програмно-апаратний комплекс «Кардіолаб» («ХАІ-Медика»). Розподіл показників оцінювався з урахуванням медіани, 25 і 75 квартилей. Для оцінки відмінностей між вибірками використовувалися непараметрический U-критерій Манна-Уїтні, а також критерій Краскелла-Уолесса. Статистично значущими вважалися відмінності між даними при значенні $p < 0,05$. Було встановлено, що чим більше ступінь зниження ТР, тим більш значущим є автономний дисбаланс, а також зниження впливу метрономізації дихання на регуляцію серцевого ритму; при значеннях ТР нижче 1000 $мс^2$ спостерігається не тільки падіння потужності парасимпатичної ланки, а й перехід від симпатикотонії до переважання нейрогуморальних факторів.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, варіабельність серцевого ритму, метрономізоване дихання

ВЛИЯНИЕ ОБЩЕЙ МОЩНОСТИ СПЕКТРА ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА НА РАСПРЕДЕЛЕНИЕ СПЕКТРАЛЬНЫХ ПОКАЗАТЕЛЕЙ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В ПРОБЕ С МЕТРОНОМИЗИРОВАННЫМ ДЫХАНИЕМ

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Для определения влияния общей мощности спектра ВСР (TP) на распределение волн высокой, низкой и очень низкой частоты 40 пациентов с артериальной гипертензией (АГ) в возрасте 58 ± 9 лет были разделены на 5 групп по степеням снижения TP на фоновом этапе пробы: 1я – более 3000 мс^2; 2я – 3000–2000 мс^2; 3я – 2000–1000 мс^2; 4я – 1000–500 мс^2; 5я – менее 500 мс^2. Для оценки показателей ВСР в каждой группе оценивались 3 этапа пробы с метрономизированным дыханием с двойным (световым и звуковым) метрономом; использовался программно-аппаратный комплекс «Кардиолаб» («ХАИ-Медика»). Распределение показателей оценивалось с учетом медианы, 25 и 75 квартилей. Для оценки различий между выборками использовались непараметрический U-критерий Манна-Уитни, а также критерий Краскелла-Уолесса. Статистически значимыми считались различия между данными при значении $p < 0,05$. Было установлено, что чем больше степень снижения TP, тем более значимым является автономный дисбаланс, а также снижение влияния метрономизации дыхания на регуляцию сердечного ритма; при значениях TP ниже 1000 мс^2 наблюдается не только падение мощности парасимпатического звена, но и переход от симпатикотонии к превалированию нейрогуморальных факторов.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, вариабельность сердечного ритма, метрономизированное дыхание

INTRODUCTION

Frequency analysis of heart rate variability (HRV) in patients with arterial hypertension (AH) provides ample opportunities to study the functional features of cardiac activity regulation, the determination of sympathovagal relationship, and the influence of neurohumoral factors on the pathological links of arterial hypertension [1–2]. The paced breathing test allows study the functional state of the cardiovascular system dynamically, which is especially important for diagnostics and monitoring of patients with AH [3–4].

One of the most important components of HRV is the total power of its spectrum (TP), which includes the full spectrum of heart rate variability frequencies, reflecting the total vegetative (autonomous) effect on the regulation of cardiac activity. According to the clinical protocols of the European Cardiology Society [5], the frequency range for TP is up to 0.4 Hz, and the normal values are defined as 3466 ± 1018 ms^2. The fluctuations of this parameter reflect the general functional state and adaptive capabilities of the organism, being an indicator of pathological changes and regulatory failures.

According to the studies [5–8] in patients with arterial hypertension, [the total power of the spectrum] TP is usually reduced, as well as the redistribution of HRV components with an increase in sympathetic and neurohumoral influences, mainly due to a decrease in the parasympathetic component of the HRV spectrum. However, studies aimed at studying the effect of reducing the total power of the HRV spectrum on the distribution of spectral components and the degree of aggravation of cardiac regulation imbalance in hypertension have not been performed.

The aim of this article is to determine the severity of sympathovagal imbalance, as well as changes in the ratio of frequency HRV parameters depending on the degree of decrease in TP in patients with essential arterial hypertension in a paced breathing test.

MATERIALS AND METHODS

40 patients (18 men, 22 women) with essential hypertension aged 58 ± 9 years were examined including: patients with AH 1 degree – 14 (35 %), AH 2 degrees – 21 (52.5 %) and AH 3 degrees – 5 (1.25 %) respectively; patients with stage I – 7 (17.5 %), stage II – 33 (82.5 %); the average duration of arterial hypetension – 6 ± 5 years. The newly diagnosed AH was detected in 1 patient (2.5 %).

Inclusion criteria: grade 1–3 arterial hypertension, stage I-II with stable angina pectoris I-III FC, chronic heart failure I-II stage I FC.

Exclusion criteria: acute myocardial infarction, unstable angina, chronic heart failure IV FC, implanted pacemakers, acquired heart valve defects, rhythm disturbances, endocrine diseases (diabetes, thyrotoxicosis, etc.), exacerbation of somatic diseases, stroke, acute hypertensive encephalopathy, vascular dementia.

The blood pressure was measured with a Microlife BP AG1-20 tonometer according to Korotkov's method. Clinical diagnosis of hypertension was made in accordance with the recommendations of the Ukrainian Association of Cardiology [9]. Calculation of HRV parameters was made using the software «Cardiolab» («HAI-Medica»).

Methods of HRV study: a test with paced (metronomized) breathing with a double (light and sound) metronome. Test conditions: test was performed in the morning hours (from 9.00 to 12.00 in a separate room with a room temperature of 20–22°C); before the test, patients abstained from smoking, drinking coffee and alcoholic beverages.

Protocol for paced breathing test:

1. Initial stage at rest – 5 minutes;
2. Deep controlled breathing with a frequency of 6 times / min – 5 minutes;
3. Recording after breathing (recovery) – 5 minutes.

In the first initial resting stage the patients were maintained at rest breathing freely in familiar to them rhythm and depth of breathing for 5 minutes to ensure that a true resting HRV values were obtained; in the second stage of paced breathing patients were instructed to perform breathing in breathing rate of 6 times per minute with additional control of visual and sound metronome for 5 minutes; in the third final resting stage the patients were breathing in a free manner for 5 minutes.

The results of the test were interpreted on the basis of international standards (protocols of the European Cardiological Society) [10]. The values of TP (total power of the HRV spectrum), low frequency wave LF (0.04–0.15 Hz), very low frequency wave VLF (< 0.04 Hz), high frequency wave HF (0.15–0.4 Hz), and LF / HF index the power of low-frequency waves to the power of high-frequency waves). These parameters were estimated in absolute and normalized units.

Depending on the degree of decrease in the TP at the initial stage of the test, the patients were divided into 5 groups: 1 – more than 3000 ms^2 was detected in 3 patients (7.5 %); 2 – 3000–2000 ms^2 in 3 patients (7.5 %); 3rd – 2000–1000 ms^2 in 12 patients (30 %); 4th – 1000–500 ms^2 in 13 patients (32.5 %); 5th – less than 500 ms^2 in 10 patients (25 %). In each group, all 3 stages of the test were evaluated.

During the statistical processing of data Microsoft Excel 7.0 software was used. In each group, the median, 25 and 75 quartiles were determined to evaluate the distribution of the parameters. To estimate the differences between the test samples, the nonparametric Mann-Whitney U test was used, as well as the *Craskell-Wallis* criterion. Statistically signify-cant differences were considered between the data at a value of $p < 0.05$.

RESULTS AND DISCUSSION

The results of the distribution of spectral HRV parameters at different levels of TP reduction in patients with arterial hypertension are presented in table 1.

In the first group of patients, low-frequency influences prevailed in the initial stage of the test ($p < 0.01$), and LF / HF values indicated a pronounced sympathicotonia (LF / HF-6.18 [3.6, 6.9]). At the same time, the contribution of low-frequency influences at this stage in groups 2, 3, 4 and 5 was less pronounced mainly due to the prevalence of waves of very low frequency (see Fig. 1). The HF parameter at the initial stage was characterized by decreased values in all study groups, which indicates the limitation of the parasympathetic component in the regulation of the heart rhythm ($p < 0.01$).

Table 1

Spectral HRV parameters depending on the TP decrease in the paced breathing test

Spectral HRV parameters	Initial stage	Paced breathing stage	Resting stage
Group 1. TP >3000			
LF, ms	2075 [1754; 2528]*	372 [303; 415.5]	1587 [1108; 2639]
VLF, ms	1479 [1383; 2416]	1000 [634; 1075]	2073 [1171; 2385]
HF, ms	272 [252; 1557]	3476 [2922;8200]	277 [193; 1272]
LF/HF	6.18 [3.6; 6.9]	0.1 [0.07; 0.105]	5.73 [3.68; 5.7]
Group 2. TP 3000-2000			
LF, ms	731 [622.5; 829.3]	153 [95.3; 483]	574 [331.5; 793]
VLF, ms	992 [930.3; 1151]	376 [150; 631.5]	686 [549.5; 1012]
HF, ms	415 [349.5; 438.3]	1567 [875; 4301]	184 [143.2; 344]
LF/HF	2.01 [1.76; 2.6]	0.11 [0.105; 0.11]	2.3 [1.6; 3.33]
Group 3. TP 2000-1000			
LF, ms	312 [256.8; 435]*	220 [156.3; 412.3]*	296 [211.3; 600]**
VLF, ms	614 [538.8; 912]*	508 [328.3; 598.5]	614 [539; 1053]*
HF, ms	203 [122.3; 246.8]*	2514 [1193; 4403]*	203 [108; 237.3]
LF/HF	2.8 [1.14; 3.12]	0.13 [0.08; 0.2]	2.7 [1.09; 3.1]
Group 4. TP 1000-500			
LF, ms	136 [109; 195]*	112 [76; 144]*	163 [122; 361]**
VLF, ms	331 [232; 404]*	346 [136; 534]	440 [280; 525]*
HF, ms	99 [37; 113]*	553 [325; 1352]*	93 [44; 160]
LF/HF	1.97 [0.88; 2.97]	0.16 [0.13; 0.26]	1.95 [1.39; 3.39]
Group 5. TP < 500			
LF, ms	86.5 [61.75; 105.8]*	74.5 [37.3; 150]*	156 [96; 241.3]**
VLF, ms	154.5 [123.8; 201]*	263 [160; 477.5]	360.5 [290; 484.8]*
HF, ms	59.5 [22.5; 112.3]*	479 [335.8; 890]*	45 [29.5; 158.3]
LF/HF	1.63 [0.97; 3]	0.15 [0.09; 0.22]	2.38 [1.8; 2.9]

*Note. * $p < 0.01$, ** $p < 0.05$.*

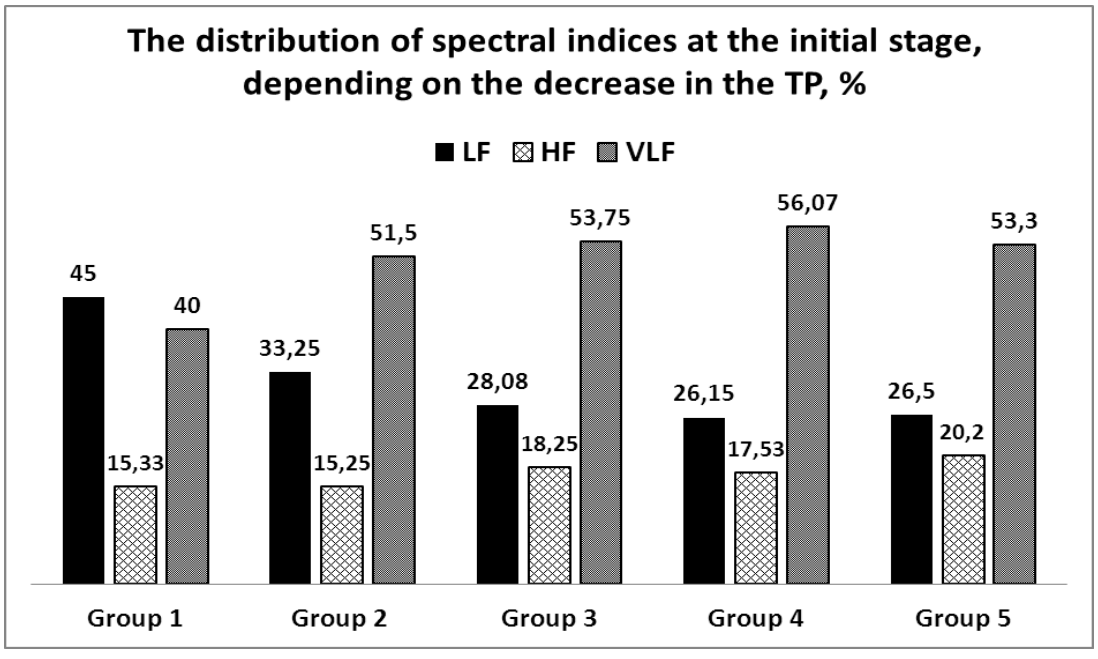

Fig. 1. Distribution of spectral parameters at the initial stage of the paced breathing test, depending on the decrease in TP, %

At the stage of metronomized breathing, high frequency waves dominated in all groups, however the intensity of the parasympathetic response to the paced breathing was not the same depending on the degree of TP decrease: thus, the maximum HF values were observed in group 1, while the lowest values were recorded in group 4 and group 5 ($p < 0.01$). As a percentage, HF in the paced breathing stage was 81.33 % in the first group, progressively decreasing in groups 2, 3, and 4; in group 5, the share of high-frequency influences was the smallest and was determined as 55.9 %; Thus, the difference between the fraction of high-frequency waves in the first and fifth group was 25.4 % (Fig. 2).

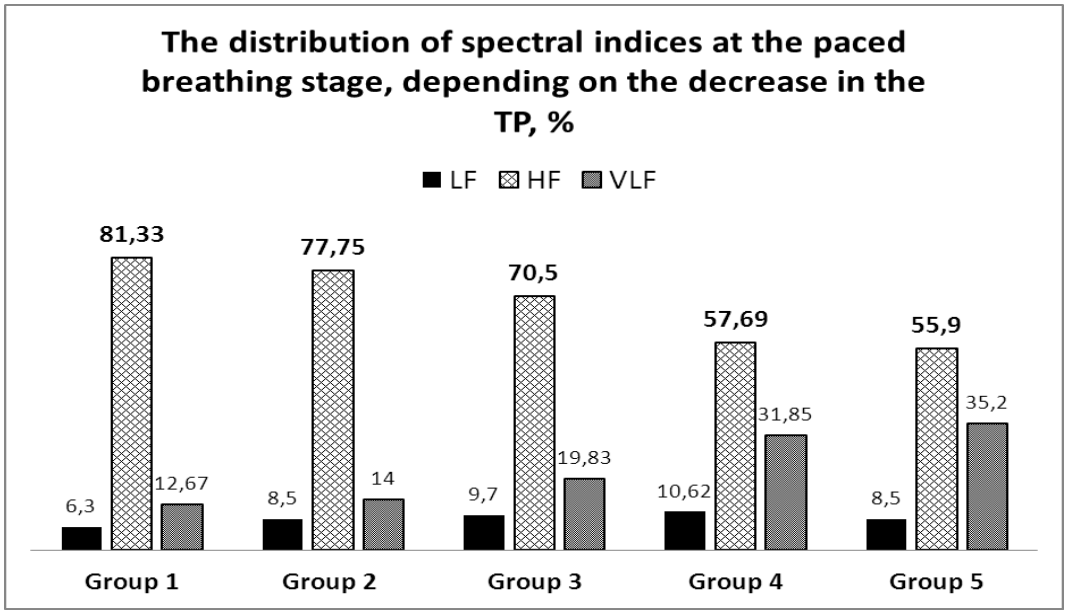

Fig. 2. Distribution of spectral indices at the stage of paced breathing, depending on the degree of decrease in TP, %

Also at this stage, along with the weakening of the parasympathetic response, there was a shift towards increasing neurohumoral influences in groups with lower TP values.

At the resting stage in group 1 low frequency waves prevailed, however sympathicotonia was less pronounced (LF / HF – 5.73 [3.68, 5.7]), mainly due to the amplification of VLF waves. The distribution of spectral indices in the remaining groups was characterized by the neurohumoral level of regulation of the heart rhythm: the proportion of very low frequency waves in these groups exceeded 50 %, while the low frequency indices were slightly lower compared to the initial stage. The HF values showed no gain at the resting stage in all study groups, a slight increase was observed in the second and fourth groups, and in group 5, characterized by the most pronounced neurohumoral effects (VLF – 59, 3 %), a decrease in the proportion of HF waves (Fig. 3).

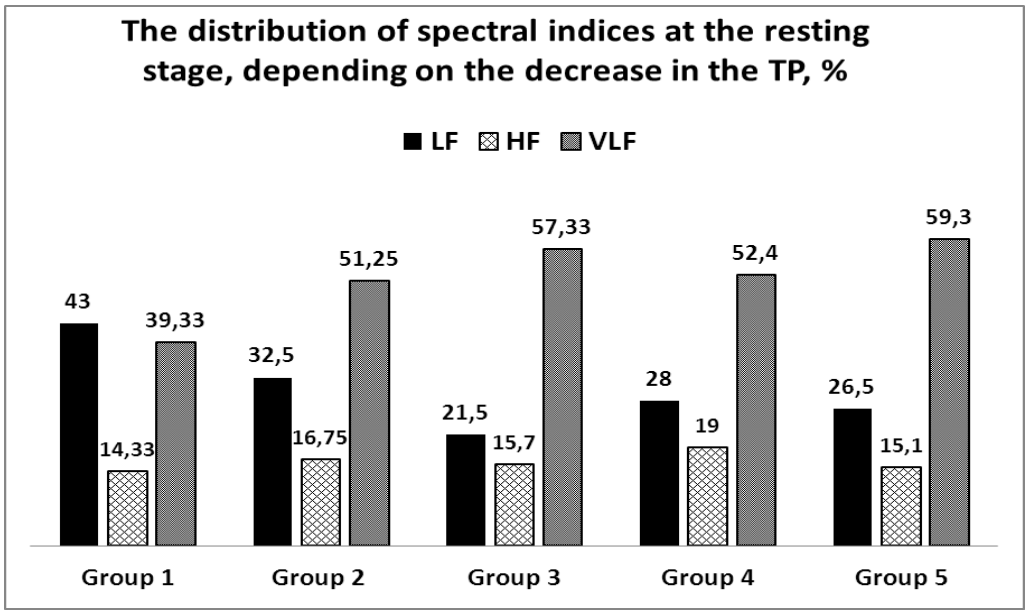

Fig. 3. Distribution of spectral parameters at the resting stage of paced breathing test, depending on the decrease in TP, %

The obtained data indicate that in patients with arterial hypertension, low and very low frequency waves play a leading role in the regulation of the heart rhythm, which is also confirmed by studies [3, 5–8]. At the same time [6–8, 11] there is a limitation of parasympathetic influences on management of cardiac activity in patients with arterial hypertension. The results of our studies confirm these data. In addition, it was found that the more the level of total power of the spectrum decreases, the less pronounced is the parasympathetic response to the paced breathing. For example, at TP values of 2000–3000 ms^2 or more, the contribution of high-frequency waves was significant (77–81 %), while at values of the total power less than 1000 ms^2, the effect of metronomized breathing on the regulation of the heart rate decreased significantly with the values of HF reflecting that (55–57 %). Simultaneously with limiting the proportion of high-frequency waves in the HRV spectrum, with a decrease in total power, there was a transition from the prevalence of sympathetic HRV components to neurohumoral mechanisms of heart rhythm regulation. Consequently, the degree of reduction in TP is an important factor associated with aggravation of autonomous imbalance and redistribution of spectral HRV parameters, which affects the prognosis and course of arterial hypertension.

Thus, research in this field is a valuable addition to the diagnostics and dynamic monitoring of patients with hypertension and is of interest for further study.

CONCLUSION

In patients with arterial hypertension, there is a tendency of decrease in the total power of the HRV spectrum, thus reflecting the decreased functional capacity of heart rhythm regulation.

The lower the degree of TP, the more significant is the disturbance of HRV regulation with a decrease in the parasympathetic component of the heart rate variability spectrum and the dominant influence of sympathetic and neurohumoral factors.

The influence of the paced breathing on the heart rhythm regulation falls depending on the decrease in the total power of the HRV spectrum: at TP values below 1000 ms^2 not only the parasympathetic component decrease is observed, but also the transition from sympathotonia to the neurohumoral factors prevalence.

Decrease in TP can be considered as an indicator of aggravation of autonomic and neurohumoral regulation.

The paced breathing test allows determine the basic level of cardiac activity regulation and dynamic disruptions in the distribution of HRV components in the metronomized breathing, as well as the possibilities for

restoring the regulatory balance of heart rate variability, which is especially important in the examination of patients with arterial hypertension.

PROSPECTS FOR FUTURE STUDIES

In the future, the study of neurohumoral factors of HRV is promising, as well as the distribution of spectral indices of cardiac rhythm variability at the stages of AH therapy.

REFERENCES

1. Yabluchanskyy N. Y., Varyabel'nost' serdechnoho rytma v pomoshch' praktycheskomu vrachu. Dlya nastoyashchykh vrachey. / N. Y. Yabluchanskyy, A. V. Martynenko – Khar'kov, 2010 – 131 p.
2. Da Silva Natália Turri. Hypertension and Autonomic Control/ Natália Turri da Silva, Thais Roque Giacon [et al.] // American Journal of Medical Sciences and Medicine. – 2014. – Vol. 2, No. 2. – p. 48–53.
3. Golubkina E. O. Assessment of changes in the distribution ratios of ultra-low-frequency, low-frequency and high-frequency components of heart rate variability during the paced breathing test in patients with arterial hypertension / E. O. Golubkina, O. O. Golubkina // Vísnik Kharkívs'kogo natsíonal'nogo unívesitetu ím. V. N. Karazína. – 2016. – Issue 31. – p. 10–17.
4. Oyeleye L. Dynamic changes in spectral heart rate variability parameters in paced breathing test in patient with uncontrolled arterial hypertension and polymorbidity / L. Oyeleye, M. Saja [et al.] // Vísnik Kharkívs'kogo natsíonal'nogo unívesitetu ím. V. N. Karazína. – 2016. – Issue 32. – p. 73–78.
5. Gorantla S. G. B. K. Heart rate variability parameters in patients with arterial hypertension in dependence on the type of daily blood pressure profile / S. G. B. K. Gorantla, O. V. Petrenko, O. V. Martynenko // Vísnik Kharkívs'kogo natsíonal'nogo unívesitetu ím. V. N. Karazína. – 2017. – Issue 33. – p. 17–22.
6. Lutfi Mohamed Faisal. Effect of blood pressure on heart rate variability / Mohamed Faisal Lutfi, Mohamed Yosif Sukkar // Khartoum Medical Journal. – 2011. – Vol. 04, Is. 1 – p. 548–553.
7. Cardiac autonomic control in adolescents with primary hypertension. [electronic resource] / [Havlíceková Z.] // Eur. J. Med. Res. – 2009. – Access to resource: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3521333/.
8. Natarajan Nirmala. A study on analysis of Heart Rate Variability in hypertensive individuals / Nirmala Natarajan, Arun Kumar Balakrishnan [et al.] // International Journal of Biomedical and Advance Research. – 2014. – Is. 5. – p. 109–111.
9. Sertsevo-sudinni zahvoryuvannya. Klasifikatsiya, standarti diagnostiki ta likuvannya kardiologichnih hvorih / Editors V. M. Kovalenko, M. I. Lutaya, Y. M. Sirenko // Ukraine Association of cardiologists, 2007, 128 p.
10. Heart rate variability. Standarts of measurement, physiological interpretation and clinical use / Task force of The European Society of Cardiologyand The North American Society of Pacing and Electrophysiology // European Heart Journal. – 1996. – Is. 17. – p. 354–381.
11. Dabrowska B. Parasympathetic Withdrawal Precedes Spontaneous Blood Pressure Elevations in Women with Primary Hypertension / B. Dabrowska, A. Dabrowski [et al.] // Cardiology. – 1996 - Vol.87, Is. 2. – p. 119–124.

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THE EFFECTIVENESS OF CHRONOTHERAPY IN HYPERTENSIVE PATIENTS WITH AN INSUFFICIENT DEGREE OF SLEEP-TIME DIASTOLIC BLOOD PRESSURE

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The violation of daily blood pressure (BP) profile is one of the predictors of cardiovascular (CV) morbidity and mortality in patients with arterial hypertension (AH). It is determined by ambulatory BP monitoring (ABPM). The aim of the study was to assess the impact of the chronotherapeutic approach on the level of systolic blood pressure (SBP) and diastolic blood pressure (DPB) and daily BP profile in patients with AH with insufficient degree of sleep-time relative DBP decline. The study included 28 patients with AH with nondipper DBP daily profile in age from 52 to 78 years old. The participants were divided onto two groups. Group 1 included 14 patients, who take all antihypertensive drugs in the morning, group 2 included 14 patients who take at least one antihypertensive drug at bedtime. All patients underwent 24-hour blood pressure monitoring using the computer system «Cardiosens» (KhAI Medica, Ukraine, with the oscillometric method of BP measurement) when enrolling in the study and after 3 months. The type of SBP and DBP diurnal profile, the mean values of SBP, DBP and hyperbaric indices were determined and compared between groups 1 and 2 at each visit, as well as within groups between visits. The results showed that morning taking of antihypertensive drugs in patients with AH with insufficient degree of DBP decline influences more on SBP while evening taking – on DBP. It was concluded that violation of DBP daily profile in medication therapy of patients with insufficient degree of DBP decline should be provided along with violation of SBP daily profile.

KEY WORDS: arterial hypertension, chronotherapy, diastolic blood pressure, nondipper

ЕФЕКТИВНІСТЬ ХРОНОТЕРАПИИ ГІПЕРТОНІЧНОЇ ХВОРОБИ У ПАЦІЄНТІВ З НЕДОСТАТНІМ СТУПЕНЕМ НІЧНОГО ЗНИЖЕННЯ ДІАСТОЛІЧНОГО АРТЕРІАЛЬНОГО ТИСКУ

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Порушення добового профілю артеріального тиску (АТ) є одним з факторів ризику серцево-судинної (СС) захворюваності та смертності у пацієнтів з артеріальною гіпертензією (АГ) і визначається методом добового моніторування АТ (ДМАТ). Метою дослідження було оцінити вплив хронотерапевтичного підходу на рівень САТ і ДАТ та добовий профіль АТ у пацієнтів з АГ з недостатнім ступенем нічного зниження ДАТ. У дослідження увійшли 28 пацієнтів з АГ з типом добового профілю ДАТ нондіпер у віці від 52 до 78 років. Учасники були розділені на дві групи. До групи 1 увійшли 14 пацієнтів, що приймають все гіпотензивні препарати вранці, в групу 2 – 14 пацієнтів, що приймають хоча б один гіпотензивний препарат на ніч. Всім пацієнтам проводилося добове моніторування АТ з використанням комп'ютерної системи «Кардіосенс» (ХАІ Медика, Україна, з осцилометричним методом вимірювання артеріального тиску) при включенні в дослідження і через 3 міс. Визначали тип добового профілю САТ і ДАТ, середні значення САТ, ДАТ і показників навантаження підвищеним тиском і порівнювали між собою в групах 1 та 2 на кожному візиті, а також всередині груп між візитами. Результати показали, що ранковий прийом гіпотензивних препаратів у пацієнтів з АГ з недостатнім ступенем нічного зниження ДАТ в більшій мірі впливає на САТ, а вечірній - на ДАТ. Були зроблені висновки, що в медикаментозної терапії пацієнтів з АГ з недостатнім ступенем нічного зниження ДАТ оцінка його добового профілю повинна проводитися нарівні з добовим профілем САТ.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, хронотерапия, діастолічний артеріальний тиск, нондіпер

ЭФФЕКТИВНОСТЬ ХРОНОТЕРАПИИ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ У ПАЦИЕНТОВ С НЕДОСТАТОЧНОЙ СТЕПЕНЬЮ НОЧНОГО СНИЖЕНИЯ ДИАСТОЛИЧЕСКОГО АРТЕРИАЛЬНОГО ДАВЛЕНИЯ

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Нарушение суточного профиля артериального давления (АД) является одним из предикторов сердечнососудистой (СС) заболеваемости и смертности у пациентов с артериальной гипертензией (АГ) и определяется методом суточного мониторирования АД (СМАД). Целью исследования было оценить влияние хронотерапевтического подхода на уровень САД и ДАД и суточный профиль АД у пациентов с АГ с недостаточной степенью ночного снижения ДАД. В исследование вошли 28 пациентов с АГ с типом суточного профиля ДАД нондиппер в возрасте от 52 до 78 лет. Участники были разделены на две группы. В группу 1 вошли 14 пациентов, принимающие все гипотензивные препараты утром, в группу 2 – 14 пациентов, принимающие хотя бы один гипотензивный препарат на ночь. Всем пациентам проводилось суточное мониторирование АД с использованием компьютерной системы «Кардиосенс» (ХАИ Медика, Украина, с осциллометрическим методом измерения АД) при включении в исследование и через 3 мес. Определяли тип суточного профиля САД и ДАД, средние значения САД, ДАД и показателей нагрузки повышенным давлением и сравнивали между собой в группах 1 и 2 на каждом визите, а также внутри групп между визитами. Результаты показали, что утренний приём гипотензивных препаратов у пациентов с АГ с недостаточной степенью ночного снижения ДАД в большей степени оказывает влияние на САД, а вечерний – на ДАД. Были сделаны выводы, что в медикаментозной терапии пациентов с АГ с недостаточной степенью ночного снижения ДАД оценка его суточного профиля должна проводиться наравне с суточным профилем САД.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, хронотерапия, диастолическое артериальное давление, нондиппер

INTRODUCTION

The violation of daily blood pressure (BP) profile is one of the predictors of cardiovascular (CV) morbidity and mortality in patients with arterial hypertension (AH) [1–3] and it is determined by ambulatory BP monitoring (ABPM). Systolic BP (SBP) is ordinarily used as ABPM index which determines the daily BP profile [4, 5]. Diastolic BP (DBP) is considered as a less important parameter despite the fact that in comparison with SBP it is regulated by the other mechanisms and that is why it has its independent prognostic and diagnostic value [6–8].

In one of our previous researches dedicated to study of daily BP profile in patients with unsatisfactory nocturnal SBP decrease it was proved that SBP and DBP profiles vary differently to each other [9]. This fact required a similar study in hypertensive patients with insufficient degree of sleep-time relative DBP decline.

OBJECTIVE

To assess the impact of the chronotherapeutic approach on the level of SBP and DPB and daily BP profile in patients with AH with insufficient degree of sleep-time relative DBP decline.

MATERIALS AND METHODS

The research was carried out within the framework of the research work «Pharmacological and interventional approaches to the treatment of patients with cardiac arrhythmias, arterial hypertension», state registration number 0116U000973.

In the settings of the outpatient clinic No. 24 in Kharkiv, 44 patients with AH aged from 41 to 78 years were examined. For further analysis, patients with an insufficient degree of sleep-time relative DBP decline (< 10 %) according to ABPM were selected.

The study included 28 people with the «nondipper» type of DBP daily profile – 19 women (68 %) and 9 men (32 %). The first stage of AH was diagnosed in 2 patients (7 %), the second – in 21 (75 %), the third – in 5 (18 %). The first degree of AH was diagnosed in 13 patients (46 %), the second – in 6 (21 %). Six patients (21 %) had controlled AH, with preserving the target values of SBP and DBP throughout the 24 hours. Nocturnal hypertension was diagnosed in 22 cases (79 %).

Participants were divided into two groups. Group 1 included 14 patients taking all antihypertensive drugs in the morning; group 2 included 14 patients taking at least one antihypertensive drug at bedtime. To achieve

target BP levels, patients, if necessary, underwent correction of antihypertensive therapy – increasing the dose, replacing or adding drugs. The regimen of antihypertensive drugs intake was not changed.

Exclusion criteria were secondary arterial hypertension, hemodynamically significant valvular heart disease, cardiomyopathy of any origin, chronic heart failure of III clinical stage or IV functional class by NYHA, any acute conditions (infections, trauma, operations) during the previous 3 months, chronic diseases in decompensated stage or exacerbation, oncological diseases, as well as any circumstances that make it difficult to perform ABPM.

All patients underwent ABPM when included in the study – 1 visit, and after 3 months – 2 visit. The monitoring was carried out using the computer system «Cardiosens» (KhAI Medica, Ukraine) with an oscillometric method of BP measurement. The monitoring was performed in the conditions of a typical patient day, with the preservation of domestic physical and psychoemotional loads. The cuff was placed on the non-dominant hand. According to Ambulatory Blood Pressure Monitoring International Recommendations 2013 [10], BP was measured with an interval of 15 minutes during the period of awake and 30 minutes during the sleep time. Periods of the day and night was defined on the basis of the patient's diary. When assessing ABPM data, in accordance with Ambulatory Blood Pressure Monitoring International Recommendations 2013 [10], manual data extraction was performed – the following measurements were excluded from the analysis:

– SBP > 250 or <70 mm Hg,

– DBP> 150 or <40 mm Hg,

– pulse pressure > 150 or <20 mm Hg;

– heart rate > 200 or <20 per minute.

The results of ABPM were excluded from analysis in the following cases:

– ≥ 30 % of invalid measurements,

– absence of BP measurements for 2 hours or more,

– unusual daily activity for the patient during monitoring,

– a night sleep period of less than 6 or more than 12 hours [10].

The degree of relative sleep-time BP decline was calculated using the formula:

(100 × [mean awake BP - mean asleep BP] / mean awake BP).

Depending on the value of this ratio the following types of daily BP profile were defined:

«dipper» – physiological decrease in BP during the night - sleep-time relative BP decline 10-20 % ;

«overdipper» – an excessive fall in BP at night, sleep-time relative BP decline > 20 %;

«nondipper» – the lack of BP reduction at night, sleep-time relative BP decline < 10 %;

«night-peaker» – night-time BP more than during daily activity, sleep-time relative BP decline < 0 [4].

The mean values of SBP, DBP and hyperbaric indices for SBP and DBP were determined for 24 hours and periods of day and night and compared in groups 1 and 2 at each visit, as well as within groups between visits.

For each ABPM parameter the arithmetic mean (M), the median (Me), and the standard deviation (Sd) were determined. Proportions of types of the daily BP profile were determined in percent (P).

A comparison of the data obtained in groups 1 and 2 at each stage of the study was performed using the unpaired Student's t-test for parameters with normal distribution and the Mann-Whitney U-test for free-distributed parameters. To compare the proportions the angular transformation method with F-test was used.

RESULTS AND DISCUSSION

The mean major values of ABMP in patients with insufficient degree of DBP decline in groups 1 and 2 on inclusion into the study are represented in table 1. At the first visit, the mean sleep-time values of SBP and DBP exceeded the recommended threshold levels in both groups during all periods of monitoring. The awake, sleep-time and daily mean values of the SBP and DBP time index (TI) were higher than normal in both groups. The percentages of controlled AH were 29 % in group 1 and 14 % in group 2 respectively (tab. 2). The high percent of nocturnal hypertension was observed in both groups (tab. 2). The daily profile of SBP and DBP in all patients from both groups corresponded to nondipper type. The comparison of studied indexes of ABMP at day time, night time and daily did not reveal significant differences between the groups (tab. 1).

Table 1

ABPM indices in patients with insufficient degree of DBP decline in groups 1 and 2, visit 1

Monitoring periods	ABPM indices	Patients groups					
		group 1			group 2		
		M	Me	Sd	M	Me	Sd
24 hours	SBP, mm Hg	134	124	24.5	138	139	15.7
	DBP, mm Hg	76	73	11.6	81	80	11.6
	SBP TI, %	43	29	34.2	62	69	31.3
	DBP TI, %	34	26	30.9	46	40	33.7
	SBP HBI, mm Hg / h	236	61	409.7	299	267	238.7
	DBP HBI, mm Hg / h	100	46	139.8	158	126	159.9
Awake	SBP, mm Hg	135	125	25.4	139	139	16.4
	DBP, mm Hg	77	75	11.9	82	80	11.8
	SBP TI, %	37	18	36.6	55	59	35.3
	DBP TI, %	26	12	31.6	39	34	35.2
	SBP HBI, mm Hg / h	139	19	267.5	166	152	153.3
	DBP HBI, mm Hg / h	50	9	85.3	81	57	101.3
Sleep- time	SBP, mm Hg	130	126	22.0	138	141	13.9
	DBP, mm Hg	74	71	11.0	78	76	10.6
	SBP TI, %	55	60	31.4	79	95	28.5
	DBP TI, %	49	43	34.4	63	64	33.9
	SBP HBI, mm Hg / h	97	42	143.9	133	118	94.3
	DBP HBI, mm Hg / h	51	31	56.7	63	35	60.0
Sleep-time relative SBP decline, %		3	4	5.5	0	1	5.4
Sleep-time relative DBP decline, %		5	7	7.0	4	5	4.0

M – mean value, Me - median, Sd – standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, TI – time index, HBI – hyperbaric index

Table 2

AH control in patients with insufficient degree of DBP decline in groups 1 and 2 at the beginning and at the end of observation

Parameters	Group 1		Group 2	
	visit 1	visit 2	visit 1	visit 2
Controlled AH	29 %	33 %	14 %	25 %
Nocturnal AH	71 %	66 %	86 %	75 %

The ABPM indices in patients with insufficient degree of DBP decline after 3 months in comparison to initial data are represented in table 3. Overall, we achieved a reduction of all ABPM parameters and target values of SBP and DBP for all monitoring periods, except sleep-time DBP, which have been reduced, but did not normalize. Statistically significant differences at the level of $p < 0.05$ were achieved for sleep-time means of DBP, DBP TI and DBP HBI. The sleep-time relative SBP decline improved insignificantly in comparison to initial data, while the sleep-time relative DBP decline was not only improved but normalized with significant differences at the level of $p < 0.05$ (tab. 3).

Table 3

Comparison of the main ABPM indices in patients with insufficient degree of DBP decline at visits 1 and 2

Monitoring periods	ABPM indices	Visits					
		visit 1			visit 2		
		M	Me	Sd	M	Me	Sd
24 hours	SBP, mm Hg	136	132	20.3	127	127	11.4
	DBP, mm Hg	79	76	11.6	73	76	7.1
	SBP TI, %	52	52	33.7	37	38	27.6
	DBP TI, %	40	30	32.3	22	12	21.7
	SBP HBI, mm Hg / h	267	161	330.6	125	115	125.0
	DBP HBI, mm Hg / h	129	55	150.3	44	28	45.2
Awake	SBP, mm Hg	137	131	21.0	129	126	13.1
	DBP, mm Hg	80	76	11.8	75	77	7.5
	SBP TI, %	46	36	36.4	28	16	30.1
	DBP TI, %	33	18	33.4	20	14	17.3
	SBP HBI, mm Hg / h	152	49	214.4	63	28	111.7
	DBP HBI, mm Hg / h	65	19	93.3	26	26	17.2
Sleep- time	SBP, mm Hg	134	131	18.4	124	129	9.9
	DBP, mm Hg	76*	73	10.9	67*	65	7.9
	SBP TI, %	67	70	31.9	53	67	36.5
	DBP TI, %	56*	56	34.3	26*	12	33.7
	SBP HBI, mm Hg / h	115	77	120.8	62	85	42.2
	DBP HBI, mm Hg / h	57*	31	57.6	18*	3	31.6
Sleep-time relative SBP decline, %		2	3	5.5	3	-1	8.6
Sleep-time relative DBP decline, %		5*	6	5.6	10*	13	7.7

M – mean value, Me – median, S – standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, TI – time index, HBI – hyperbaric index p< 0.05*

The ABPM indices in patients with insufficient degree of DBP decline in groups 1 and 2 after 3 months are represented in table 4. At the second visit in group 1 daily and awake SBP and DBP target values were achieved, while sleep-time SBP and DBP means normalization was failed though its decline was achieved. In group 2 at the second visit decline and normalization of target SBP and DBP values were achieved during all the periods of observation except sleep-time related SBP decline. In group 1 the values of SBP HBI have declined in comparison to initial data and the mean awake-time values of SBP HBI were normalized. Mean daily values and mean awake-time values of DBP were nearly unchanged and the sleep-time DBP values have even improved. In group 2 the SBP HBI values decline was achieved and DBP HBI values were restored to borderline or normal levels.

The changes of daily SBP and DBP profile in patients with insufficient degree of DBP decline in groups 1 and 2 after 3 months are given in table 5. The normalization of daily SBP profile in group 1 was achieved in 2/3 of patients. At the second visit in group 2 the improvement of sleep-time relative SBP decline was achieved but the normalization of daily SBP profile wasn't in any patient of this group (tab. 4, 5).

The types of daily DBP profile (dipper, nondipper and overdipper) distributed evenly between all patients in group 1 at the second visit (tab. 5). In the group 2 the values of sleep-time relative DBP decline were adjusted in accordance with dipper type: the normalization of daily DBP profile was observed in a half of patients of this group (tab. 4, 5). In both groups at the second visit the number of patients with nocturnal AH was decreased while the percent of patients with controlled AH was increased. These

changes are more significant in the group 2 (tab. 2).

There were no statistically significant differences in group 1 between first and second visit. In group 2 statistically significant decrease of sleep-time DBP values and sleep-time relative DBP decline in comparison to initial data at the level of $p < 0.05$ was achieved along with decrease of sleep-time values of DBP HBI at the level of $p < 0.01$ (tab. 4).

Table 4

ABPM indices in patients with insufficient degree of DBP decline in groups 1 and 2, visit 2

Monitoring periods	ABPM indexes	Patients groups					
		group 1			group 2		
		M	Me	Sd	M	Me	Sd
24 hours	SBP, mm Hg	126	127	1.2	128	126	16.0
	DBP, mm Hg	78	76	4.0	70	69	7.0
	SBP TI, %	29	38	15.1	43	39	35.6
	DBP TI, %	34	37	29.5	13	11	10.8
	SBP HBI, mm Hg / h	78	107	58.1	160	121	158.9
	DBP HBI, mm Hg / h	67	58	66.9	26	24	13.5
Awake	SBP, mm Hg	126	126	2.5	130	125	18.2
	DBP, mm Hg	80	78	3.8	72	71	8.5
	SBP TI, %	17	16	3.2	36	20	40.0
	DBP TI, %	25	27	22.0	16	10	15.1
	SBP HBI, mm Hg / h	19	19	9.1	96	30	146.5
	DBP HBI, mm Hg / h	27	28	25.3	25	22	12.8
Sleep- time	SBP, mm Hg	126	129	8.5	122	125	11.9
	DBP, mm Hg	74*	71	8.3	63*	64	3.2
	SBP TI, %	51	67	40.7	55	65	39.4
	DBP TI, %	49	52	44.0	9	11	6.0
	SBP HBI, mm Hg / h	60	88	49.8	63	77	43.6
	DBP HBI, mm Hg / h	39	30	42.0	2**	2	1.1
Sleep-time relative SBP decline, %		7.5	10	11.5	6	4	9.2
Sleep-time relative DBP decline, %		8	8	6.8	12^{i}	13	8.7

M - mean value, Me - median, Sd - standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, TI – time index, HBI – hyperbaric index; $^{*}p < 0,05$ comparing groups 1 and 2 at visit 2; $^{i}p < 0,05$ comparing visits 1 and 2 of group 2; $^{**}p < 0,01$ comparing visits 1 and 2 of group2.

In group 2 the SBP and DBP levels in all periods of monitoring were reduced to a greater extent than in group 1. Particularly, the mean daily and awake relative DBP values are increased in comparison to the first visit though they still remain within the normative values. The mean sleep-time relative DBP values stay unchanged.

The lower values of DBP ABMP indices at the second visit were achieved in group 2. In group 1 the lower values of ABMP indices at the second visit were noticed in parameters that refer to SBP.

Sleep-time relative SBP decline increased approximately equally in groups 1 and 2 (+4.5 % and +5.6 % respectively) (tab. 1, 4). The normalization of daily SBP profile in group 1 was achieved in 2/3 of patients while in group 2 its normalization was achieved in none of the patients (tab. 5).

Sleep-time relative DBP decline increased more in group 2 in comparison to group 1 (+8 % and +3 % respectively) (tab. 1, 4). The normalization of daily DBP profile was achieved in most of patients in group 2. In group 1 the daily DBP profile changed to overdipper type in 1/3 of patients (tab. 5).

Table 5

BP daily profiles in patients with insufficient degree of DBP decline in groups 1 and 2 at the first and second visits

Daily profile type		Group 1		Group 2	
		visit 1	visit 2	visit 1	visit 2
SBP	**dipper**	0	67 %	0	0
	nondipper	100 %	33 %	100 %	100 %
	overdipper	0	0	0	0
DBP	**dipper**	0	33 %	0	50 %
	nondipper	100 %	33 %	100 %	50 %
	overdipper	0	33 %	0	0

DISCUSSION

The change in the paradigm of the importance of DBP as a risk factor for CV events in the late 90s of the last century led to the fact that in the overwhelming majority of cases only the daily SBP profiles are estimated [4, 5] and very little attention is given to daily DBP profiles [6].

We also did not find studies on the effect of AH chronotherapy on the daily DBP profile.

The obtained data show that the morning intake of antihypertensive drugs in patients with AH with insufficient degree of sleep-time relative DBP decline has a greater impact on SBP, and the evening intake – on DBP, which can be explained by differences in the mechanisms of their regulation [7].

In accordance with this, it is not enough to focus only on the daily SBP profile in the treatment of patients with AH.

CONCLUSIONS

1. The antihypertensive therapy in patients with insufficient degree of sleep-time relative DBP decline, regardless of the regimen of medications, leads to SBP and DBP levels decrease with normalization of their daily profiles.

2. The results of the therapy depend on the time of antihypertensive drugs intake, and the morning reception reduces the SBP to a greater extent, and the evening one – DBP.

3. In the pharmacotherapy of patients with AH with insufficient degree of sleep-time relative DBP decline, the assessment of its daily profile should be carried out along with the daily SBP profile.

PROSPECTS FOR FUTURE STUDIES

It seems advisable to compare the effects of chronotherapy in patients with insufficient degree of sleep-time relative SBP decline and patients with insufficient degree of sleep-time relative DBP decline.

REFERENCES

1. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring / [G. Parati, G. Stergiou, E. O'Brien et al.]. // Journal of Hypertension. – 2014. – Vol. 32(7). – P. 1359–1366.
2. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) // Journal of Hypertension. – 2013. – Vol. 31, Is. 7. – P. 1281–1357.
3. Prognostic Effect of the Nocturnal Blood Pressure Fall in Hypertensive Patients: The Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) Meta-Analysis. / [G. F. Salles, G. Reboldi, R. H. Fagard et al.]. // Hypertension. – 2016. – Vol.67. – P. 693–700.
4. Heart rate variability in patients with hypertension, comorbid with peptic ulcer disease, taking into account circadian systolic blood pressure / [O. E. Tomina, O. Y. Bichkova, G. M. Fomych et al.]. // The journal of V. N. Karazin` KhNU, Series «Medicine». – 2012. – Issue 24. – P. 52–62.

5. Efficacy of cormobid octeoarthrosis with arterial hypertension control considering the types of orthostatic reactions and circadian profiles of arterial pressure / I. V.Soldatenko, N. V. Lysenko, O. E. Tomina, V. L. Kulyk. // The journal of V. N. Karazin` KhNU, Series «Medicine». – 2013. – Issue 25. – P. 47–53.
6. Ambulatory Hypertension Subtypes and 24-Hour Systolic and Diastolic Blood Pressure as Distinct Outcome Predictors in 8341 Untreated People Recruited From 12 Populations / [Yan Li, Fang-Fei Wei, Lutgarde Thijs et al.]. // Circulation. – 2014. – Vol. 130. – P. 466–474.
7. O'Rourke M. Mechanical principles in arterial disease / O'Rourke. // Hypertension. – 1995. – Vol. 26. – P. 2–9.
8. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study / [S. S. Franklin, V. A. Lopez, N. D. Wong et al.]. // Circulation. – 2009. – Vol. 119. – P. 243–250.
9. Petrenko O. V. The effectiveness of chronotherapy in hypertensive patients with an insufficient degree of sleep-time systolic blood pressure decline / O. V. Petrenko, M. I. Yabluchansky. // The journal of V. N. Karazin` KhNU, Series «Medicine». – 2017. – Vol. 34. – P. 19–26.
10. 2013 ambulatory blood pressure recommendations for the Diagnosis of Adult Hypertension, Assessment of Cardiovascular and other Hypertension-associated Risk and Attainment of Therapeutic Goals // Chronobiology International. – 2013. – Vol. 30 (3). – P. 355–410.

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PROGNOSTIC VALUE OF P-SELECTIN IN PATIENTS WITH STABLE ANGINA PECTORIS

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Coronary artery disease for many years is being the main cause of death in many developed countries. Currently, cardiovascular disease (CVD) plays the main role in the evolution of the total mortality in the world. Most deaths occur as a result of coronary heart disease (more than 300 thousand per year). It is known that chronic inflammation is a marker of global endothelial dysfunction and may be associated with the increased risk of cardiovascular events in patients with coronary artery disease. Nowadays, it is very promising in terms of assessing the prognosis and course of the disease to study P-selectin.

KEY WORDS: angina pectoris, P-selectin, clopidogrel, inflammation

ПРОГНОСТИЧНЕ ЗНАЧЕННЯ РІВНЯ Р-СЕЛЕКТИН У ХВОРИХ НА СТАБІЛЬНУ СТЕНОКАРДІЮ

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ІХС протягом багатьох років є головною причиною смертності населення в багатьох економічно розвинених країнах. В даний час серцево-судинні захворювання (ССЗ) відіграють вирішальну роль в еволюції загальної смертності у світі. Найбільше смертей настає внаслідок ішемічної хвороби серця - понад 300 тис. випадків на рік. Відомо, що хронічне запалення є маркером розвитку глобальної ендотеліальної дисфункції і може бути пов'язане з підвищеним ризиком розвитку серцево-судинних ускладнень у хворих на ішемічну хворобу серця. На сьогоднішній день, дуже перспективним щодо оцінки прогнозу і перебігу захворювання є Р-селектін.

КЛЮЧОВІ СЛОВА: стабільна стенокардія, Р-селектин, клопідогрель, хронічне запалення

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ УРОВНЯ Р-СЕЛЕКТИНА У БОЛЬНЫХ СТАБИЛЬНОЙ СТЕНОКАРДИЕЙ

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ИБС в течение многих лет является главной причиной смертности населения во многих экономически развитых странах. В настоящее время сердечно-сосудистые заболевания (ССЗ) играют решающую роль в эволюции общей смертности в мире. Больше всего смертей наступает вследствие ишемической болезни сердца – более 300 тыс. случаев в год. Известно, что хроническое воспаление является маркером развития глобальной эндотелиальной дисфункции и может быть связано с повышенным риском развития сердечно-сосудистых осложнений у больных с ИБС. На сегодняшний день, очень перспективным в отношении оценки прогноза течения заболевания является Р-селектин.

КЛЮЧЕВЫЕ СЛОВА: стабильная стенокардия, Р-селектин, клопидогрель, хроническое воспаление

INTRODUCTION

Despite the optimal therapy, which has significantly reduced the cardiovascular mortality in industrialized countries, it remains at a sufficiently high level [1]. One of the most promising directions for further reducing the «residual» cardiovascular risk is the reduction of systemic inflammation [2]. To date, high-sensitivity C-reactive protein is used as a standard for assessing the level of systemic inflammation, which is not inferior

in terms of prognostic significance for adverse outcomes to LDL cholesterol [3], however, various mechanisms that take place through the systemic inflammatory response different cell types that produce cytokines, chemokines, adhesion molecules, which may not have the same degree of activation in patients [4]. One of the ways of individualizing therapy for patients with high cardiovascular risk is the evaluation of new biomarkers, including P-selectin, reflecting at the individual level different ways of activating the systemic inflammatory response. Based on this, a study of the prognostic value of the P-selectin level for large adverse events in patients with stable angina may provide new opportunities in reducing the «residual» cardiovascular risk.

OBJECTIVE

The aim of the study is to study the prognostic value of the P-selectin level for adverse outcomes in patients with stable angina.

MATERIALS AND METHODS

The study included 89 patients, 27 of them women and 62 men aged 38 to 89 years (mean age 63.2 ± 11.8 years), who had stable angina on the basis of clinical manifestations, these stress tests and coronaroangiography in accordance with the recommendations of the European Society of Cardiology 2013 [5].

Patients included in the study were tested in addition to standard methods to determine the level of a new biomarker of P-selectin inflammation and a reference marker of systemic inflammation, high-sensitivity CRP (hs-CRP). For the quantitative determination of P-selectin, a set of reagents «Human sP-selectin Platinum ELISA» was used. The minimum detectable concentration of P-selectin was 0.2 ng/ml. For the quantitative determination of hs-CRP, a set of reagents «SRB-IFA-Best (highly sensitive)» was used. The determined concentration of CRP was 0.1-10 mg/l. Specificity of the assay was provided by the use of monoclonal antibodies, which are highly specific for CRP.

All patients underwent standard therapy in accordance with these recommendations, except in cases of contraindications and intolerance of the drugs. The presence of adverse cardiovascular events was assessed prospectively in 3 years from the inclusion of patients in the study at the total end point (cardiovascular death, nonfatal myocardial infarction, unstable angina, ischemic cerebral stroke, transient ischemic attack, revascularization). To compare the differences between groups with different initial levels of P-selectin, the Kaplan-Meier procedure was used to construct the cumulative survival curves.

RESULTS AND DISCUSSION

In general, in the group of patients with verified stable angina, the average P-selectin level in plasma was 90.0 + 46.5 ng/ml and hs-CRP 6.2 + 4.2 mg/l. In the correlation analysis, no correlation was found between the plasma levels of P-selectin and hs-CRP in the examined patients ($r = -0.131$, $p = 0.284$). A weak negative correlation between the indices did not reach certainty.

After three years, myocardial infarction with ST segment elevation in 3 patients, acute coronary syndrome (unstable angina) was recorded in 9 patients, 2 patients underwent revascularization of coronary vessels, ischemic stroke in 3 patients was diagnosed and 2 patients died due to cardiovascular diseases.

The analysis was performed on the total primary endpoint in patients, depending on the initial level of P-selectin. Patients were divided into groups depending on the initial level of P-selectin: more and less median and on tertili.

When comparing 2 groups of patients with P-selectin level, more and less median revealed a tendency (Fig. 1), which did not reach the significance, to a greater number of cardiovascular events in patients with P-selectin level above the median.

In the cumulative analysis of events in patients divided into groups according to the trotyl, depending on the initial level of P-selectin (Fig. 2), it was found that the number of events in group 1 patients (lower tertile in P-selectin level) was significantly lower than in patients patients of group 3 (upper tertile by the initial level of P-selectin).

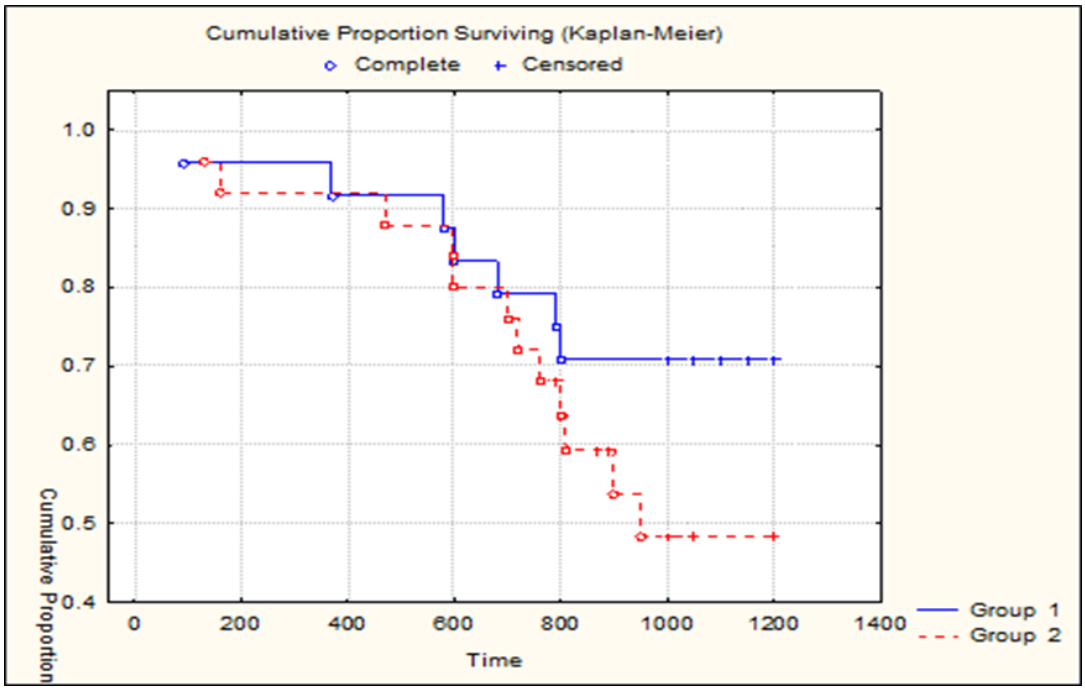

Fig. 1. Comparison of the cumulative number of events in patient groups, depending on the initial level of P-selectin (Kaplan-Meier procedure). Group 1 – patients with a P-selectin level below the median, group 2 – patients with a P-selectin level above the median (significance of differences between groups p = 0.29).

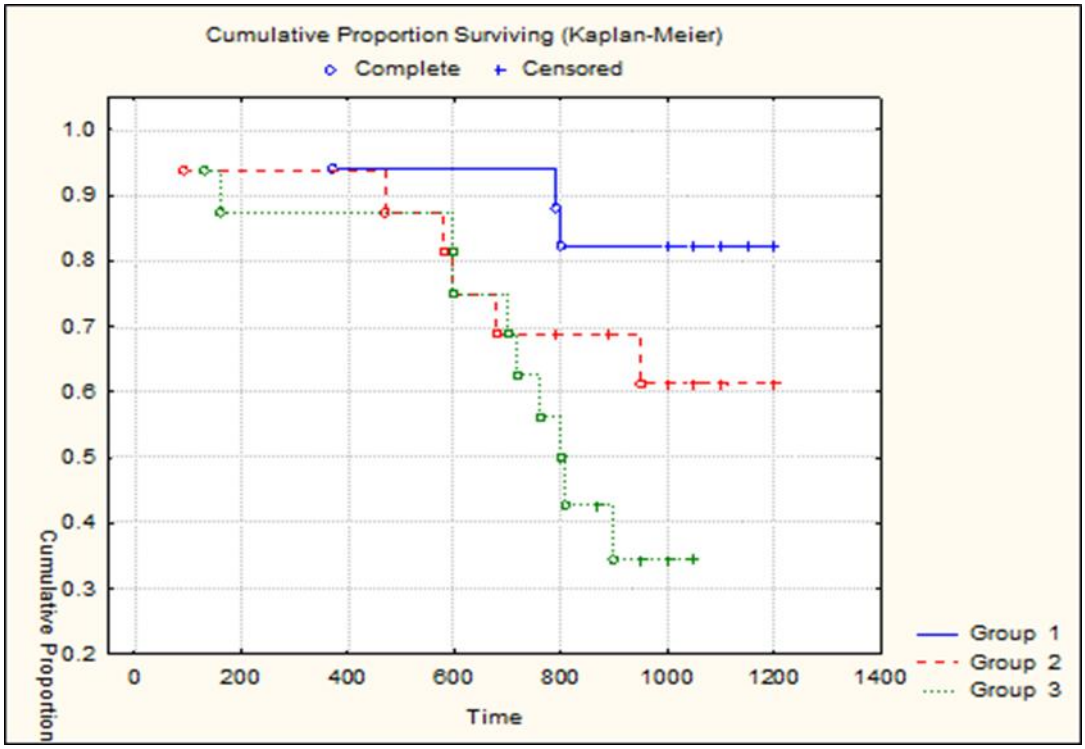

Fig. 2. Comparison of the cummulative number of events in patient groups, depending on the initial level of P-selectin (Kaplan-Meier procedure). Group 1 – patients with P-selectin level in the lower tertile, group 2 – patients with patients with P-selectin level in the middle tertile, group 3 – patients with P-selectin level in the upper tertile (significance of differences between groups 1 and 3 – p = 0.046).

Thus, a significantly greater number of cardiovascular events in patients with a high baseline P-selectin level (upper tertile) were found compared with a lower level (lower tertile). Given the lack of correlation between the level of P-selectin and the standard biomarkerhs-CRP, this creates the perspective not only for obtaining additional prognostic information in patients with angina with the help of P-selectin level estimation, but also for use in the therapy of specific inhibitors of various cytokines, chemokines, molecules adhesion, etc., which is confirmed by randomized studies using inclucumab [6] and kanakinumab [7].

However, experimental data should be taken into account that the soluble P-selectin studied in our study is only a marker of the platelet component of the inflammatory response, and its dimeric form is the active mediator [8].

CONCLUSIONS

1. The level of P-selectin in patients with stable angina is not associated with the level of hs-CRP, which creates the prerequisites for the personalization of therapeutic goals for reducing the systemic inflammatory response.

2. In patients with high P-selectin (upper tertile), significantly more cardiovascular events are observed compared to patients with low P-selectin (lower tertile), which makes it possible to use the P-selectin level to estimate the prognosis in patients with stable angina.

3. The data obtained in the study allow in the long term to use a new biomarker of inflammation of P-selectin to estimate the prognosis in patients with stable angina and to personalize therapy of patients with coronary heart disease aimed at reducing the «residual» cardiovascular risk associated with the activation of various mechanisms of the systemic inflammatory response.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study the level of P-selectin drug in patients with stable angina with correction of the frequency and doses of antiplatelet agents.

REFERENCES

1. European Society of Cardiology: Cardiovascular Disease Statistics 2017. Atlas Writing Group, Timmis A., Townsend N., Gale C., Grobbee R., Maniadakis N., Flather M., Wilkins E., Wright L., Vos R., Bax J., Blum M., Pinto F., Vardas P. Eur Heart J. – 2017. Nov 27.
2. Ridker P. M. How Common Is Residual Inflammatory Risk? CircRes. – 2017. Feb 17; 120 (4):617–619.
3. Ridker P. M. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. CircRes. – 2016. Jan 8; 118 (1):145–56.
4. Swirski F. K., Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science. – 2013. Jan 11; 339 (6116):161–6.
5. ESC 2013 guidelines on the management of stable coronary artery disease // European Heart Journal. – 2013. – Vol. 34. – P. 2949–3003. URL: http://www.unimarburg. de/fb20/allgprmed/aktuelles/leitlinie.pdf
6. Tardif J. C., Tanguay J. F., Wright S. R., Duchatelle V., Petroni T., Grégoire J. C., Ibrahim R., Heinonen T. M., Robb S., Bertrand O. F., Cournoyer D., Johnson D., Mann J., Guertin M. C., L'Allier P. L. Effects of the P-selectin antagonist in clacumab on myocardial damage after percutaneous coronary intervention for non-ST-segment elevation myocardial infarction: results of the SELECT-ACS trial. // J Am CollCardiol. – 2013. May 21; 61 (20): 2048–55.
7. Ridker P. M., Everett B. M., Thuren T., Mac Fadyen J. G., Chang W. H., Ballantyne C., Fonseca F., Nicolau J., Koenig W., Anker S. D., Kastelein J. J. P., Cornel J. H., Pais P., Pella D., Genest J., Cifkova R., Lorenzatti A., Forster T., Kobalava Z., Vida-Simiti L., Flather M., Shimokawa H., Ogawa H., Dellborg M., Rossi P. R. F., Troquay R. P. T., Libby P., Glynn R. J. CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. // N Engl J Med. – 2017. Sep 21; 377 (12): 1119–1131.
8. Gross P. L. Soluble P-selectin is the smoke, not the fire. Blood. – 2017. Jul 13; 130 (2): 101–102.

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PREVALENCE OF POLYMORPHISM OF THE TLR-9 TYPE GENE IN PATIENTS WITH CHRONIC EPSTEIN-BARR VIRUS INFECTION

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The prevalence of polymorphism -1486T/C of the TLR-9 gene was studied in 44 patients with chronic Epstein-Barr virus infection (CEBV). The control group for the study of the polymorphisms prevalence of -1486T/C of the TLR-9 gene was 40 healthy donors. Three main genotypes of -1486T/C of the TLR-9 gene were identified based on the obtained results – TT, TC, CC. Investigation of the occurrence frequency of individual genotypes revealed the dominance of the TC genotype, compared with the homozygous TT and CC genotypes. The study of -1486T/C of the TLR-9 gene polymorphism frequency distribution for different genotypes demonstrated the specificity of changes in the TC genotype in patients with CEBV and the absence of such for the TT and CC genotypes. These results confirm the important role of the TLR-mediated signaling in the pathogenesis of the disease, which is necessary to determine the genetic background associated with the course of the disease and its possible consequences. These are the aspects that will further enable the identification of risk groups among such patients and provide timely therapy.

KEY WORDS: chronic Epstein-Barr virus, Toll-like receptors, polymorphism, prevalence

ПОШИРЕНІСТЬ ПОЛІМОРФІЗМУ ГЕНУ TLR-9 ТИПУ У ХВОРИХ З ХРОНІЧНИМИ ФОРМАМИ ЕПШТЕЙНА-БАРР ВІРУСНОЇ ІНФЕКЦІЇ

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Досліджено поширеність поліморфізму -1486T/C гену TLR-9 у 44 пацієнтів з хронічними формами Епштейна-Барр вірусної інфекції (ХЕБВ). Контрольна група для вивчення поширеності поліморфізму -1486T/C гена TLR-9 становила 40 здорових донорів. На підставі отриманих результатів виявлено три основних генотипи -1486T/C гену TLR-9 – TT, TC, CC. Аналіз частоти зустрічаємості окремих генотипів виявило домінування генотипу TC, порівняно з гомозиготним генотипами TT та CC. Вивчення розподілу частот зустрічаємості поліморфізму -1486T/C гену TLR-9 для різних генотипів продемонструвало специфічність змін для генотипу TC у хворих з ХВЕБ та відсутність таких для генотипів TT та CC. Ці результати підтверджують важливу роль TLR-опосередкованої сигналізації у патогенезі даного захворювання, що є необхідним для визначення генетичного фону, пов'язаного з перебігом хвороби та можливими наслідками ХВЕБ. Саме ці аспекти в подальшому дозволять визначати групи ризику серед таких пацієнтів та провести своєчасну терапію.

КЛЮЧОВІ СЛОВА: вірус Епштейна-Барр, Толл-подібні рецептори, поліморфізм, поширеність

РАСПРОСТРАНЕННОСТЬ ПОЛИМОРФИЗМА ГЕНА TLR-9 ТИПА У БОЛЬНЫХ С ХРОНИЧЕСКИМИ ФОРМАМИ ЭПШТЕЙНА-БАРР ВИРУСНОЙ ИНФЕКЦИИ

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Исследована распространенность полиморфизма -1486T/C гена TLR-9 среди 44 пациентов с хроническими формами Эпштейна-Барр вирусной инфекции (ХВЭБ). Контрольная группа для изучения распространенности полиморфизма -1486T/C гена TLR-9 составила 40 здоровых доноров. На основании полученных результатов выявлено три основных генотипа -1486T/C гена TLR-9 – TT, TC, CC. Анализ частоты встречаемости отдельных генотипов выявил доминирование генотипа TC по сравнению с гомозиготными генотипами TT и CC. Изучение распределения частот встречаемости полиморфизма -1486T/C гена TLR-9 для разных генотипов показало специфичность изменений для генотипа TC у больных с ХВЕБ и отсутствие таковых для генотипов TT и CC. Эти результаты подтверждают важную роль TLR-опосредованной сигнализации в патогенезе данного заболевания,

что необходимо для определения генетического фона, связанного с течением болезни и возможными последствиями ХВЭБ. Именно эти аспекты в дальнейшем позволят определить группы риска среди таких пациентов и провести своевременную терапию.

КЛЮЧЕВЫЕ СЛОВА: вирус Эпштейна-Барр, Толл-подобные рецепторы, полиморфизм, распространенность

INTRODUCTION

To date, scientists have proved that the immune response to the presence of an infectious agent in the human body depends on the type of immunity that is the inherited system of protection against pathogens [1–3]. Toll-like receptors (TLRs) are the major signal receptors that are expressed intracellularly and overhead cells: neutrophils, macrophages, dendritic cells, endothelial and epithelial cells, and natural killers (NK) [3–5].

11 TLRs are indicated in mammals, 10 of them are found in humans. The effector cells of the innate immunity express all 10 types of TLRs, each of which binds to the specific ligand [3]. Numerous experimental studies, as well as accumulated results derived from clinical practice, have convincingly proved the key role of Toll-like receptors in the pathogenesis of immunopathological diseases [6–7].

Recognition of bacterial structures (lipopolysaccharide, lipoproteins, peptidoglycan, flagellin etc.) occurs through the activation of TLR-1, 2, 4, 5 and 6 [3, 7]. Four TLR receptors are capable of recognizing nucleic acids – TLR-3, 7, 8, and 9, TLR-7 and TLR-8 recognize their own and viral single-stranded RNAs, and TLR-9 binds to unmethylated bacteria DNA. TLR-3 is capable of recognizing double-stranded RNA viruses, so this receptor has a key role in the antiviral immune response [3, 8].

Recent studies have made it possible to establish that one of the main causes that may affect the TLR immune response in infectious pathology is the polymorphism of the encoded genes. There is growing evidence that single-nucleotide polymorphism (SNP), due to the formation of specific gene alleles, makes an important contribution to the phenotypic differences among humans, including the individual features of the protective reactions development, as well as the susceptibility to a number of diseases [9–11].

Differences in genes that control the protective response of the body can determine the different course nature of the inflammatory response and specific immunological reactions in contact with foreign structures. First of all it concerns the genes of regulatory molecules that provide the initial stages of the development of inflammatory reactions: pathogen recognition, intracellular activation signal, and the synthesis of inflammatory mediators [5].

Polymorphism of genes suggests that several variants can be copied from the same gene and be structurally different from the copy of the same protein, some of copied variants are either not active, or have the opposite function [12, 13]. Regarding TLR-polymorphism, it has been found that it can lead to a disruption of the infectious agent's recognition, an imbalance in the functioning of the innate immunity system, increased sensitivity to infections and the development of chronic inflammatory processes. Other studies show that the polymorphism of TLR genes due to severe interference with the immune response can determine the severity of the infectious process course, which assumes the nature of the systemic inflammatory response, as well as the development of thanatogenesis [3, 13].

All genes of the TLR-9 subfamily are encoded by two exons. The amino acid sequences of TLR-7 and TLR-8 have a similarity of 72.7 %. These amino acids are encoded by genes that are 42.3 % identical and localized on the X chromosome (Chr22). The TLR-9 gene is on the short shoulders of the third chromosome (3r21.3) and is bound to genes such as MYD88 and CAMP that are in the region containing tumor growth genes [13]. The protein products of all of the genes mentioned above play an important role in the reactions of innate immunity either in direct protection (LL-37) or in signals conduction in the cell (MyD88, NF-kB).

Different works emphasize the polymorphism association of the TLR-2 and TLR-9 genes with infectious diseases. It is known that such polymorphism of the TLR-2 gene as Arg753Gln, T597C is associated with infections caused by Candida albicans, M. tuberculosis, cytomegalovirus (CMV), herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) and others pathogens [8, 11, 14–15]. The polymorphism of the TLR-9 gene, that

includes G1174A, G1635A and A2848G, is associated with systemic lupus erythematosus, the development of an infection caused by HIV-1 and other diseases [8]. Listed above polymorphisms are located both in the LRR domain of the TLRs that recognizes the pathogen and in the TIR domain involved in the signal in the cell.

A number of studies have demonstrated the role of TLR in the pathogenesis of Lyme disease. Lipoproteins of Borrelia, in particular OspA, potentially activate inflammatory response by binding to CD14 and TLR-2 expressed on macrophages. As a result, TLR-2, TLR-6, TLR-1/2, TLR-5, and TLR-9 receptors induce the secretion of macrophage mediated proinflammatory cytokines. The TLR-2/TLR-6, TLR-2/TLR-1 receptor dimers are involved in the activation of the nuclear transcription factor NfkB through the recognition of triacylated lipoproteins, such as Borrelia burgdorferi OspA, flagellin, peptidoglycans and zymosan [3, 8, 13].

Edyta Paradowska et al. investigated the polymorphism of genes (-1237T/C, rs5743836; -1486T/C, rs187084, 1174G/A, rs352139 and 2848C/T, rs352140) among 72 children with CMV infection in their work. The authors established an increased frequency of heterozygous -1486 T/C and 2848 C/T genotypes of TLR-9 in infants with CMV infection compared with non-infected cases. The heterozygous variants of these two SNPs increased the risk of CMV disease in children. The obtained data indicate that -1486 T / C and 2848 C / T polymorphisms of TLR-9 may be a genetic risk factor for the development of CMV-induced infection [16].

However, there is an insufficient amount of conducted studies on the prevalence of different types of TLR gene polymorphism in patients with EBV infection in the contemporary scientific literature.

OBJECTIVE

Investigate the frequency of the 1486T/C polymorphism of TLR-9 gene in patients with chronic Epstein-Barr virus infection (CEBV).

MATERIALS AND METHODS

The study had been performing at the Department of General and Clinical Immunology and Allergology of the Medical Faculty of Kharkiv National University named V. N. Karazin and clinical base of the Department – Regional Clinical Hospital of Infectious Diseases, in Kharkiv during 2009–2016 in the framework of the research topic: «Study of the role of immune, autoimmune and metabolic disorders in the pathogenesis and consequences of the infection process caused by herpes viruses» No. 0112U005911 of state registration.

Complete blood count and biochemical profile were carried out for all patients in the dynamics of the disease. The material for the study was the serum of patients with Epstein-Barr virus (EBV) infection, which was obtained during the period of the disease. Blood for research was collected from the elbow vein in the amount of 10 ml in a sterile Eppendorf tube.

Specific antiviral antibodies (VCA-IgM, EA-IgM and EBNA-IgG) in serum were determined by the solid phase enzyme-linked immunosorbent assay (ELISA) with production sets produced by Vector-Best (Novosibirsk, Russian Federation) and IBL (Hamburg, Germany) according to the instructions given. Some patients were serologically screened for HSV-1, HSV-2, CMV, toxoplasma, hepatitis viruses (A, B and C), and HIV for differential diagnosis. For this purpose, the following test systems for solid-phase ELISA were used: anti-HAV-IgM, anti-CMV-IgM, anti-Toxo-IgM, HBsAg, anti-HCV-total and anti-HIV-1 + 2-total, produced by: «Vector-Best» (Novosibirsk, Russian Federation), «IBL» (Hamburg, Germany).

«AmpliSens» reagents sets (Moscow, Russian Federation) were used for the detecting the DNA of the EBV by PCR with reverse transcription with hybridization and fluorescence detection of amplification products. The isolation of the DNA from the specimens was carried out using a kit for DNA extraction made by the «Miniprep» (Sillex M, Russia) using the method of sorption of DNA on sorbent by Boom R. et al., 1990. DNA amplification was performed using the kit «DNA amplification» (Silex-M, Moscow) on the BIC amplifier.

Genomic DNA was isolated using the «Plasma/serum DNA/RNA extraction kit» (LitTech, Russia).

A polymorphic site of -1486 T/C, rs187084 of the TLR9 gene was found by real-time PCR amplification by determining the restriction fragment length (RFLP)-PCR using Ncol restriction enzymes and oligonucleotide primers. DNA primers for target genes were

selected using the GeneRunner v.3.0 program and synthesized by the LitTech, Russia.

The serum concentrations of the studied cytokines (CK): IJI-lβ, TNF-α, IL-6, IL-2, IL-4, IL-10 were determined using the test systems made by the «Protein Contour» Ltd (Saint-Petersburg, Russian Federation), using the manufacturer's instructions and solid-phase ELISA.

The results of the research were processed by the method of variation and correlation statistics using the Statistika 10.0 for Windows program (Stat Soft Inc, USA). The average arithmetic (M), the mean square deviation (σ) and the average error of the arithmetic mean (m) were calculated for each variation series. Methods of parametric and nonparametric statistics were also used. Quantitative and qualitative analysis of intra-system and inter-system correlation connections were carried out using the method of correlation structures and the sequential analysis of Wald.

The distribution of genotypes was determined by applying the Hardy-Weinberg Law, the population genetics law, which allows assessing the population risk of genetically determined diseases, since each population has its own set of allele fund and, accordingly, a different frequency of unfavorable alleles. The distribution of the investigated polymorphic genotypes was checked for compliance with the Hardy-Weinberg equilibrium using the $\chi 2$ criterion.

The comparison of the frequencies of alleles and genotypes between the groups was carried out by analyzing the conjugation tables using the Fisher's exact test. The odds ratio (OR) was calculated with a 95 % confidence interval (CI) in order to compare the frequency of variants in unbound groups. Relative risk of disease and complications was estimated using the OR parameter. The OR and 95 % confidence intervals was calculated using Odds ratio calculator. The indicator $OR = 1$ was considered as a lack of association; $OR > 1$ – as a positive association («predisposition»), $OR < 1$ – as a negative association of allele or genotype with the disease.

RESULTS AND DISCUSSION

Diagnosis CEBV was conducted by clinical symptoms, complaints and laboratory results. Clinical signs that indicate active virus infection: fever, lymphadenopathy, presence of chronic inflammatory lesions in the oropharynx and nasopharynx, asthenia symptoms were taken into account. In addition, the severity and features of the mononucleosis syndrome were assessed, and the presence of concomitant pathology manifestations was taken into account.

The provisions of the World Medical Association Declaration of Helsinki, Code of Ethics of a doctor of Ukraine, informing the patient about the nature of the study were adhered during the study. The clinical diagnosis of the patients included in the study was defined as B27 according to the International statistical classification of diseases, 10th revision (version 2007). The verification of the clinical diagnosis of infectious mononucleosis (IM) in patients older than 18 years was conducted in accordance with the recommend-dations of Zh. I. Vozianova et al. (2001).

The criteria for selecting patients in the CEBV group were such complaints as fatigue, general weakness, emotional lability, depressive states, insomnia, headache, chills, throat discomfort, and muscle pain. In the clinical examination, attention was paid to the enlargement of lymph nodes, subfebrile fever, hyperemia of the oropharynx. In some patients, hepatosplenomegaly was noted.

Etiotropic therapy included valacyclovir 1000 mg 3 times a day in different groups and immunomodulatory drug allokin-alpha 1.0 ml subcutaneously once every two days (course 6 injections). The effectiveness of the therapy was assessed in patients with EBV infection on the basis of clinical data, achievement of biochemical, laboratory and virological remission (disappearance of the DNA of the EBV or decrease of the level of viremia).

Characteristic of the main clinical forms in patients with CEBV is presented in Table 1.

Analysis of the data presented in the table 1 allowed to establish that the most frequent clinical syndrome among patients with CEBV was asthenovegetative, which manifested in patients complaints about a general weakness in 69 % of cases, fatigue in 73 %, headache in 85 %, sleep disorders in 45 %, and respiratory tract involvement in the form of tonsillitis and pharyngitis more than 3 times a year in 72 %. Lymphadenopathy syndrome was found in 121 patients with CEBV. It was characterized predominantly by an enlargement of anterior and posterior lymph nodes. Clinical symptoms of arthralgia, myalgia, neuralgia and meningeal symptoms were diagnosed in 49.7 % of patients

with CEBV. The syndrome of subfebrile condition was characterized by body temperature variations during the day from 37.2 °C to 37.5 °C and was observed in 90 patients with CEBV. And hepatolial syndrome was confirmed in this category of patients only in almost 10 % of cases.

Table 1

Characteristics of the main clinical forms in patients with HBEB

Clinical symptoms	Absolute quantity (n = 183)	Interest (%)
Asthenovegetative syndrome	183	100
Damage of lymphoid tissue of the pharynx	132	72
Peripheral lymphadenopathy	121	66,1
Arthralgia, myalgia, neuralgia	91	49,7
Durable subfebrile	90	49,1
Hepatolial syndrome	18	9,8

In most patients, clinical trial data indicated polymorphism and nonspecific clinical manifestations, however, they last ones were characterized by persistence and durability.

Indicators in the complete blood count were characterized by the normal amount of leukocytes, the average number of which was 5.7 ± 1.9×109/l. Lymphocytosis and monocytosis were indicated in more than 2/3 of patients with CEBV, that is 64.7 % and 62.4 % respectively. The average percentage of lymphocytes was 39.5 ± 2.1 %, and monocytes – 11.3 ± 0.9 %, respectively.

Research to determine polymorphism -1486T/C of TLR-9 gene was conducted on 44 patients with CEBV. Among them, women amounted to 25 (56.8 %), men – 19 (43.2 %) aged from 18 to 44 years. The control group for studying the prevalence of – 1486T/C polymorphism of TLR-9 gene consisted of 40 healthy donor individuals. The average age was 24.2 ± 2.4 years, in the range from 18 to 44 years.

Distribution of patients and healthy people by age and gender is presented in Table 2.

The following genotypes -1486T / C gene TLR-9 – TT, TS, CC were obtained as a result of the molecular-genetic survey of 44 patients with CEBV and patients of the control group.

Table 2

Distribution of surveyed by age and gender, abs. number, (%)

Age, years	**Patients with CEBV (n = 44)**				**Control (n = 40)**			
	men		**women**		**men**		**women**	
	n	%	n	%	n	%	n	%
18–24	4	21,1	7	28	10	45,4	9	50
25–34	10	52,6	10	40	6	27,3	5	27,8
35–44	5	26,3	8	32	6	27,3	4	22,2
Total:	19	43,2	25	56,8	22	55	18	45

The frequency of distribution of the 1486T/C SNP in TLR-9 gene in patients with CEBV was as follows: TT genotype – 11 % (5 patients), TC – 73 % (32 patients) and CC – 16 % (7 patients). In the control group, the wild type genotype TT was detected in 40.0 % (16 patients), the heterozygous genotype TC – in 45.7 % (18 patients), while the homozygous CC genotype was found in 14.3 % (6 patients).

It should be noted that the homozygous CC genotype was verified almost with the same frequency among the groups of patients being studied, while the homozygous TT genotype, on the contrary, was more frequently found in the control group of patients. The heterozygous TC genotype was significantly often verified in the group of patients with CEBV (Fig. 1).

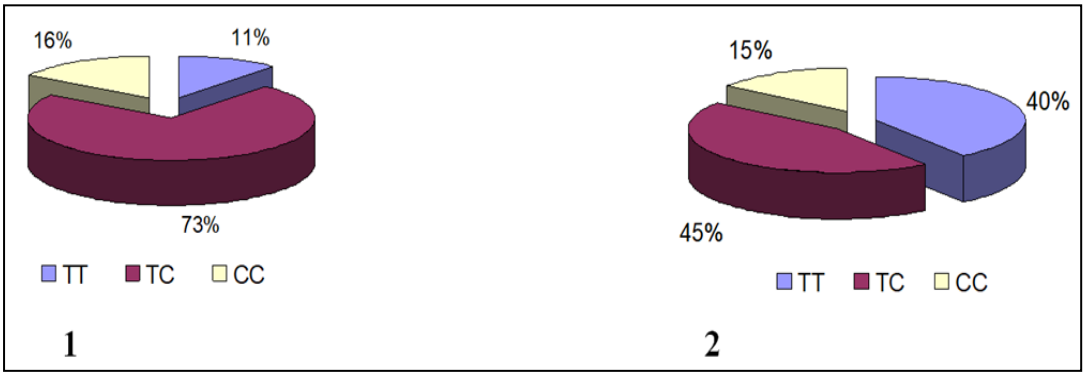

Fig. 1. Frequency of individual genotypes -1486 T/C TLR-9 gene in patients with HBEB (1) and control group (2)

The occurrence frequency of -1486T/C genotype of the TLR-9 gene – TT, TC, CC are given in Table 3 in the form of percent (P) ± standard deviation of the percentage (SdP for binomial distribution) and the results of the Student's t-test.

As can be seen from the table, the occurrence frequency of TT-1486T/C genotype TLR-9 gene differed significantly in comparison to the same data of the control group and was 11 ± 31 versus 40 ± 49 ($p < 0.05$). Also, the studied index was statistically significantly different from that of the control group for the TC genotype and was 73 ± 44 and 45 ± 50 ($p < 0.05$). There was no statistically significant difference in the incidence rate of the CC-1486T/C genotype TLR-9 gene from the control group's parameters – 16 ± 37 versus 15 ± 36 ($p > 0.05$).

Table 3

The frequency of genotypes -1486 T / C TLR-9 gene - TT, TS, SS, P (%) ± σ

TLR-9 rs187084 C/T	Patients with CEBV (n=44)	Control (n = 40)
TT	11 ± 31 [1]	40 ± 49
TC	73 ± 44 [1]	45 ± 50
CC	16 ± 37	15 ± 36

Note:
1 – Reliable probability from the control group at p-value < 0.05

The distribution of the occurrence frequencies of genotypes for patients with CEBV and patients in the control group are given in table 4 according to the results of statistical analysis.

Statistically significant differences at $p < 0.05$ were found for the genotypes of TT and TC in the group of patients with CEBV and control group through the analysis of the frequency distribution of genotype -1486 T/C TLR-9 gene in patients with IM. Thus, for the homozygous genotype of TT, this indicator was 11 % vs. 40 % ($p < 0,05$), for the genotype TC 73 % vs. 45 % ($p < 0,05$), whereas for the CC genotype, the frequency distribution did not have statistically significant differences compared to the control group and was found in the studied groups of patients with the same frequency of 16 % vs. 15 % ($p > 0.1$).

Table 4

Distribution of genotype frequencies -1486 T/C TLR-9 gene in patients with CEBV

TLR-9 rs187084 C/T	Patients with CEBV (n = 44)	Control (n = 40)	Fischer's criterion	OR (odds ratio)	95 % CI
TT	5 (11 %)	16 (40 %)	p < 0,05	0,19	0,06–0,59
TC	32 (73 %)	18 (45 %)	p < 0,05	3,26	1,3–8,1
CC	7 (16 %)	6 (15 %)	p > 0,1	1,07	0,33–3,5

According to the calculated odds ratio, the presence of the heterozygous TC genotype (CI: 1.3–8.1 and OR = 3.26, respectively) in the genome of patients with CEBV is specific for patients with CEBV, that allows it to be assessed as a positive association, compared to the obtained indices for homozygous TT types (CI: 0.06–0.59 and OR = 0.19) and the CC genotype (CI: 0.33–3.5 and OR = 1.07, respectively) that are evaluated as a negative association of genotypes with chronic forms of EBV infection.

We analyzed the frequency of individual allelic variations, depending on the type of immune response to determine the effect of the 1486 T/C of TLR-9 gene on the production of proinflammatory and anti-inflammatory CK.

Data on the detection of a combination of alleles in patients with CEBV are presented in table 5.

Two types of immune response: dissociative, which was characterized by a slight increase in proinflammatory IL-1β, TNF-α, IL-6 and regulatory IL-2 and a significant increase in anti-inflammatory IL-4 and IL-10; and hyporeactive – low concentrations of both proinflammatory and anti-inflammatory CK were found according to the levels of the CK in 80 patients with CEBV. Dissociation type was detected in 58.7 % (47 patients) with CEBV, the hyporeactive type was found in 41.3% (33 patients), from the total number of subjects. A study to determine the effect of 1486T/C polymorphism of the TLR-9 gene was performed on 44 patients with CEBV.

Table 5

Occurrence frequency of allelic variations of 1486T/C gene of TLR-9 gene in patients with CEBV with different types of immune response (n, %)

Type of immune response (n=44)	TT		TC		CC	
	abs.	%	abs.	%	abs.	%
Dissociative type (n=28)	1	2,3	20	45,5	7	15,9
Hyporeactive type (n=16)	4	9,1	12	27,3	–	–
Total:	5	11,4	32	72,8	7	15,9

As can be seen from Table 5, the frequency of T-alleles detection was 84.1 % (37 patients) on CEBV, the incidence of C-alleles was 88.6 % (39 patients).

Data analysis of table 5 and fig. 2 allowed establishing that the heterozygous TC genotype was found to be the dominant genotype among patients with CEBV, which was found in 71.4 % of patients with dissociation type of immune response and in 75 % of patients with hyporeactive type of immune response.

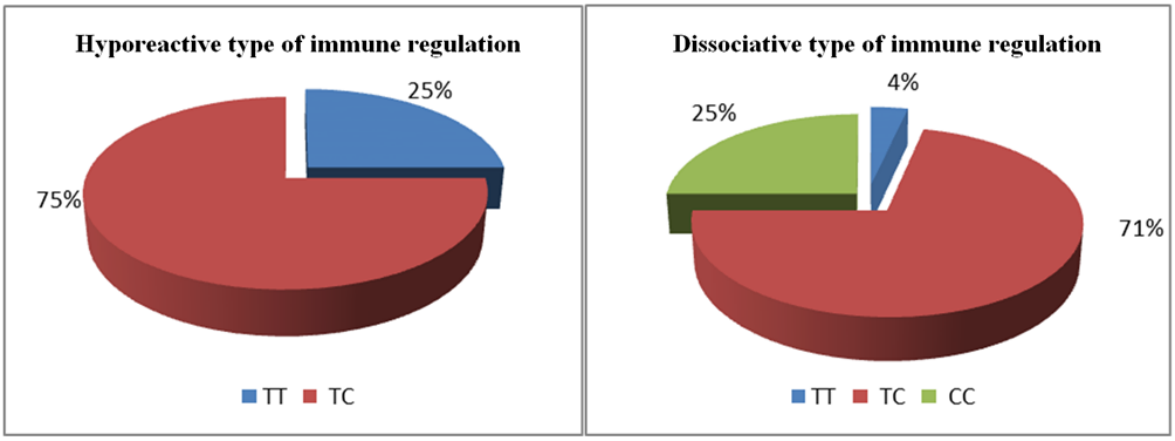

Fig. 2. Occurrence frequency of allelic variations of 1486T/C gene of TLR-9 gene in patients with CEBV with different types of immune response (%)

CONCLUSIONS

The analysis of the results of the -1486T/C polymorphism of the TLR-9 gene revealed three main genotypes – TT, TC, CC. Investigation of the occurrence frequency of individual genotypes revealed the dominance of the genotype TC, compared with the homozygous genotypes of TT and CC. The study of frequency distribution of the polymorphism -1486T/C of TLR-9 for different genotypes demonstrated the specificity of changes in the TC genotype and the absence of such in the TT and CC genotypes in patients with CEBV.

Our study for the purpose of determining the 1486T/C polymorphism of the TLR-9, that is associated with chronic forms of CEBV infection, confirms the important role of TLR-mediated signaling in the pathogenesis of this disease, which is necessary to determine the genetic background associated with the course of the disease and possible consequences of CEBV. These aspects will further enable the identification of risk groups among such patients and provide timely therapy.

Analysis of the results allowed establishing the following:

1. The 1486T/C polymorphism of the TLR-9 gene is significantly more frequent in patients with CEBV than in the control.

2. The frequency distribution of the -1486T/C polymorphism of the TLR-9 gene allowed the establishment of the association of the genotype TC with chronic forms of the EBV infection, which is very specific for this group of patients.

PROSPECTS FOR FUTURE STUDIES

It seems advisable to study differences in the immune response, the development of complications and the activity of the process in patients with CEBV and various 1486T/C polymorphism of TLR-9 gene in patients with chronic Epstein-Barr virus infection (CEBV) and drug correction depending on the results.

REFERENCES

1. Brubaker S. W. et al. Innate immune pattern recognition: a cell biological perspective // Annual review of immunology. – 2015. – V. 33. – p. 257–290.
2. Lester S. N., Li K. Toll-like receptors in antiviral innate immunity // Journal of molecular biology. – 2014. – V. 426. – No. 6. – p. 1246–1264.
3. Kawai T., Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors // Nature immunology. – 2010. – V. 11. – No. 5. – p. 373.
4. Kawasaki T., Kawai T. Toll-like receptor signaling pathways // Frontiers in immunology. – 2014. – V. 5. – p. 461.
5. De Nardo D. Toll-like receptors: Activation, signaling and transcriptional modulation // Cytokine. – 2015. – V. 74. – No. 2. – p. 181–189.
6. Achek A., Yesudhas D., Choi S. Toll-like receptors: promising therapeutic targets for inflammatory diseases // Archives of pharmacal research. – 2016. – V. 39. – No. 8. – p. 1032–1049.
7. Satoh T., Akira S. Toll-Like Receptor Signaling and Its Inducible Proteins // Microbiology spectrum. – 2016. – V. 4. – No. 6.
8. Beima-Sofie K. et al. Toll-like receptor 9 polymorphism is associated with increased Epstein–Barr virus and Cytomegalovirus acquisition in HIV-exposed infants // Aids. – 2018. – V. 32. – No. 2. – p. 267–270.
9. Skevaki C. et al. Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious diseases // Clinical & Experimental Immunology. – 2015. – V. 180. – No. 2. – p. 165–177.
10. Schnetzke U. et al. Polymorphisms of Toll-like receptors (TLR2 and TLR4) are associated with the risk of infectious complications in acute myeloid leukemia // Genes and immunity. – 2015. – V. 16. – No. 1. – p. 83.
11. Lai Y. F. et al. Functional polymorphisms of the TLR7 and TLR8 genes contribute to Mycobacterium tuberculosis infection // Tuberculosis. – 2016. – V. 98. – p. 125–131.
12. Drutskaya, M. S. Vrozhdennoye raspoznavaniye virusov [Tekst] / M. S. Drutskaya, P. V. Belousov, S. A. Nedospasov // Molekulyarnaya biologiya. – 2011. – V. 25, No. 3. – p. 7–19.
13. Barton, G. M. Viral recognition by Toll-like receptors [Text] / G. M. Barton // Seminars in Immunology. – 2007. – Vol. 19, Issue 1. – P. 33–40.
14. Choteau L. et al. Role of TLR1, TLR2 and TLR6 in the modulation of intestinal inflammation and Candida albicans elimination // Gut pathogens. – 2017. – V. 9. – No. 1. – p. 9.

15. Mukherjee S., Karmakar S., Babu S. P. S. TLR2 and TLR4 mediated host immune responses in major infectious diseases: a review //Brazilian Journal of Infectious Diseases. – 2016. – V. 20. – No. 2. – p. 193–204.
16. Paradowska, E. TLR9 -1486T/C and 2848C/T SNPs Are Associated with Human Cytomegalovirus Infection in Infants [Text] / E. Paradowska, A. Jabłońska, M. Studzińska, K. Skowrońska, P. Suski, M. Wiśniewska-Ligier et. al. // PLOS ONE. – 2016. – Vol. 11, Issue 4. – P. e0154100.

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TO THE PROBLEM OF COMORBIDITY AND SYNTHROPY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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The study objective is to establish the relationships features between lipid profile and other parameters of homeostasis in case of chronic obstructive pulmonary disease in framework comorbidity with coronary artery disease and arterial hypertension.

Materials and methods: the lipid profile, CRP, IgE, HbA_1C, FEV_1, Tiffno's index and SpO_2 in 35 patients with chronic obstructive pulmonary disease (groups B, C, D), that were studied by standard methods.

Results: A large quantity of correlations between different indicators that increased in relation to disease progression and presence of comorbidity was found. Cluster analysis confirmed the affinity between these indicators.

Conclusion: A large quantity of correlation links between lipids and other indices of homeostasis and the results of cluster analysis indicate the development of adaptation and disadaptation processes under such circumstances as elevation of hypoxia in chronic obstructive pulmonary disease and these might be evaluated as synthropy of comorbidity with coronary artery disease and arterial hypertension.

KEY WORDS: chronic obstructive pulmonary disease, lipid profile, comorbidity, synthropy

ЩОДО ПРОБЛЕМИ КОМОРБІДНОСТІ ТА СИНТРОПІЇ ПРИ ХРОНІЧНОМУ ОБСТРУКТИВНОМУ ЗАХВОРЮВАННІ ЛЕГЕНЬ

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Мета роботи – встановити особливості взаємодії ліпідного спектру з іншими показниками гомеостазу при коморбідності хронічного обструктивного захворювання легень із ішемічною хворобою серця та гіпертонічною хворобою.

Матеріали й методи: у 35 пацієнтів із хронічним обструктивним захворюванням легень (групи B, C, D) досліджені показники ліпідного спектру, рівні СРБ, IgE, HbA_1C, ОФВ 1, індекс Тифно та SpO_2 стандартними методами.

Результати: Виявлено велику кількість кореляційних зв'язків між різними показниками, кількість яких зростає при прогресуванні хвороби та коморбідності. Кластерний аналіз підтвердив наявність спорідненості між цими показниками.

Заключення. Велика кількість кореляційних зв'язків між ліпідами та іншими показниками гомеостазу, результати кластерного аналізу свідчать про розвиток процесів адаптації та дезадаптації в умовах наростаючої гіпоксії при хронічному обструктивному захворюванні легень і можуть бути оцінені як синтропія при коморбідності з ішемічною хворобою серця та гіпертонічною хворобою.

КЛЮЧОВІ СЛОВА: хронічне обструктивне захворювання легень, ліпідний профіль, коморбідність, синтропія

К ПРОБЛЕМЕ КОМОРБИДНОСТИ И СИНТРОПИИ ПРИ ХРОНИЧЕСКОМ ОБСТРУКТИВНОМ ЗАБОЛЕВАНИИ ЛЕГКИХ

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Цель работы – установить особенности взаимодействий липидного спектра с другими показателями гомеостаза при коморбидности хронического обструктивного заболевания легких с ишемической болезнью сердца и гипертонической болезнью.

Материалы и методы: у 35 пациентов с хроническим обструктивным заболеванием легких (группы B, C, D) исследованы показатели липидного спектра, уровни СРБ, IgE, HbA_1C, ОФВ 1, индекс Тиффно, SpO_2 стандартными методами.

Результаты: Обнаружено большое количество корреляционных связей между различными показателями, нарастающее по мере прогрессирования болезни и при коморбидности. Кластерный анализ подтвердил наличие сродства между этими показателями.

Заключение. Большое количество корреляционных связей между липидами и другими показателями гомеостаза, результаты кластерного анализа свидетельствуют о развитии процессов адаптации и дезадаптации в условиях нарастающей гипоксии при ХОЗЛ и могут оцениваться как синтропия при коморбидности с ишемической болезнью сердца и гипертонической болезнью.

КЛЮЧЕВЫЕ СЛОВА: хроническая обструктивная болезнь легких, липидный профиль, коморбидность, синтропия

«When we are examining an adult patient,
we rarely meet with one pathological form;
generally, the presented pathological facts
have different origin in time and reason.»
S. Botkin

INTRODUCTION

Interest into the problem of comorbidity and synthropy in various diseases is increasing nowadays [1–7]. This interest is explained by new data in the interrelations of a genome and a phenome which evolve depending on environmental conditions. The concept of «diseasome» is introduced, which means the whole complex of inherited diseases, including their genes and the ability to express these genes. It is a complex network of links between diseases and genes that determine them, the integration of all genetic disorders (disease phenome) and the network of disease genes (disease genome) [8]. Syntrophic genes, which are responsible for the development of comorbid diseases, are identified. Neutral genetic markers that determine the predisposition to diseases are also identified. Studies are existed to prove the presence of specific adverse alleles of genes that determine the development of cardio-respiratory pathology in chronic obstructive pulmonary disease (COPD), occupational lung diseases, and bronchial asthma [9].

The achievements of molecular biology, genomics and molecular genetics have deepened our understanding about human diseases, taking into consideration all factors contributing to the development of the disease, from a network approach to genome, phenome and diseasome associations. At the same time genes take various functional positions in the network of interaction [10]. Comorbid states were an incentive for studying general mechanisms of pathogenesis of various diseases [6]. The numerous connections between lifestyle and environmental influences on physiological, clinical, molecular, and genetic levels were discovered in large-scale cohort studies. They have provided a new under-standing of health, premorbid and multimorbid conditions.

Synthropy reflects the tendency of living organisms functioning to achieve higher levels of vital activity organization in new conditions and creates a special phenotype of the disease. It supposes the necessity of a holistic, personified approach to the prevention, diagnosis, treatment and prognosis of the disease, studying of universal network interactions at the genomic, molecular, cellular levels. From the synthropy position this approach can ensure the development of «networked» pharmacotherapy taking into account emergence, constantly arising new pathogenetic properties and connections at certain phases in the disease evolution [11].

OBJECTIVE

Study of relationships features between lipid profile and other parameters of homeostasis at COPD in framework comorbidity with coronary artery disease (CAD), arterial hypertension (AH) and type 2 diabetes mellitus (DM).

MATERIALS AND METHODS

Integrative principles were used to design study: 32 parameters of homeostasis were studied, 9^{th} of which were studied in the

treatment process (oxygen saturation (SpO_2), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), Tiffno's index (FEV_1/FVC ratio), reversibility test of airways obstruction with bronchodilator agent, results of CAT and mMDR questionnaires).

35 COPD patients (57.14 % male and 42.68 % female) aged from 42 to 82 years, the average age was 57.0 [54.0–67.0] suffering from COPD exacerbation and comorbid pathology were examined according to standard protocols. The average COPD duration was 10.02 [5.0–15.0] years.

All patients underwent clinical examination, assessment of complete blood count, clinical urine test, and sputum analysis, carbohydrate metabolism and determine level of creatinine, IgE, and C – reactive protein (CRP).

Fasting concentration of total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL) and very low density lipoproteins (VLDL) were carried out via standard biochemical methods. Climov's formula was used to count atherogenic index (AI). The level of total IgE was determined with chemiluminescent immunoassay method. Determination of the serum concentration of CRP was performed by immunoturbidimetric method. Glomerular filtration rate (GFR) was evaluated via Cockcroft-Gault formula.

The pulmonary function test (PFT) was performed by using a computer spirograph («Spirocom», Scientific and Technical Center of Radioelectronic Devices and Technologies, Kharkov, UA). Bronchodilator reversibility was measured in a half an hour after inhalation of salbutamol 0.4 mg.

The statistical analysis was carried out by using nonparametric methods of the package Statistica 10. The data are represented by the median (Me) with interquartile range (Me [25 %–75 %]), unless otherwise indicated. The relationship between the variables was estimated with Spearman's rank-order correlation ($p < 0.05$). Cluster analysis with complete linkage was performed.

RESULTS AND DISCUSSION

According to design of our study the parameter of lipid profile (TC, TG, HDL, LDL, VLDL, and AI) and their correlation with other studied parameters are presented in the article.

The comorbidity was noted in 23 COPD patients, 11 COPD patients type 2 DM was diagnosed, 8 COPD patients had CAD (cardiosclerosis, stable angina), and 4 COPD patients had AH II stage.

According to the classification proposed by GOLD 2014, patients were divided into 3 groups: group B-12 patients, group C-14 patients, group D-9 patients. The prevalence of the comorbid diseases in each group were: in group B 8.33 % of patients did not have accompanying pathology, 16.6 % had AH, 16.6 % had CAD, 58.33 % had AH combined with CAD (in 3 – postinfarction cardiosclerosis). In group C 21.43 % of patients did not have accompanying diseases, CAD were found in 28.7 % of patients and 50 % of patients had AH associated with CAD. Comorbid pathology was found in all patients group D: 22.22 % had CAD and 77.78 % had AH combined with CAD.

A comparative analysis of the lipid profile (Table) indicates a tendency for an increase in LDL and AI at comorbidity with CAD (in comparison with the group without CAD). These differences are especially pronounced for TC and TG ($p < 0.05$).

The lowering of VLDL in the group with CAD mismatches from the overall trend. A tendency towards increase TC, TG, VLDL, LDL and decrease in HDL was determined in COPD patients with hypertension as well.

It should be borne in mind while interpreting the shifts of the lipid spectrum that TGs are an important energy substrate, cholesterol is a component of cell membranes and intracellular organelles. These lipids are water insoluble and transferred in the composition of lipoproteins, complexes of lipids with specific proteins (apolipoproteins). VLDL transport endogenous TG from the liver to other tissues, LDL provide cholesterol transport from the liver to peripheral tissues, HDL are associated with reverse transport from peripheral tissues to the liver, from where it can be eliminated. Thus all lipoproteins are in a dynamic state and between them there is an intensive exchange of lipids and proteins.

Table

Comparative characteristic of lipid profile depends on presence of comorbid pathology

	COPD	COPD with CAD	COPD without CAD	COPD with AH	COPD without AH
TC, mmol/l	6.20 [4.80–6.45]	6.20 [5.3–6.5]	5.70* [4.80–6.40]	6.34 [4.80–6.34]	6.13 [5.45–6.78]
HDL, mmol/l	1.21 [1.12–1.37]	1.30 [1.15–1.37]	1.14 [1.12–1.18]	1.23 [1.12–1.37]	1.30 [1.15–1.40]
TG, mmol/l	2.76 [1.47–3.22]	2.78 [1.46–3.24]	1.69* [1.55–2.70]	2.80 [1.46–3.24]	2.12 [1.53–2.99]
LDL, mmol/l	3.70 [3.0–4.22]	3.96 [3.20–4.22]	3.45 [2.44–3.68]	4.20 [2.44–4.22]	3.96 [3.21–4.39]
VLDL, mmol/l	0.85 [0.48–1.13]	0.82 [0.53–1.13]	0.94 [0.48–1.10]	1.10 [0.53–1.10]	0.94 [0.30–1.45]
AI	3.47 [2.86–4.50]	3.55 [3.03–4.50]	3.55 [2.55–4.43]	3.55 [2.60–4.50]	3.35 [3.04–4.58]

*Note: * – significant difference between the indices in the COPD group with CAD and without CAD ($p < 0.05$).*

V. J. Marshall [12] recommends distinguishing «ideal» and «abnormal» lipid levels in serum. The levels of TC and TG in all groups of examined patients were elevated in comparison with the «ideal» ones, TG level was «abnormally» high (more than 2.5 mmol/l) either in whole group of COPD patients or at comorbidity with AH or CHD (3.2 mmol/l, 2.8 mmol/l, 3.2 mmol/l, respectively).

Significant changes in the number of correlations between different indices of homeostasis were found depending on the clinical group of COPD: the number of significant correlations was 94 in group B, in group C – 134, in group D – 112 ($p < 0.05$). This may be associated with an intensification of the adaptation processes to the disease in group C and the subsequent depletion of compensatory mechanisms in group D. Similar trends were observed at comorbidity with CAD (in the group of CAD the number of correlations was 156, in the group without CAD – 71) and at comorbidity of AH (in the group with AH the number of correlations was 159, without AH – 109).

The analysis of statistically significant interrelationship with the lipid profile in the whole group of COPD patients revealed a moderate uphill relationship between TC and CRP (R = 0.55) indicating the lipids participation in the development of systemic inflammation. 14 correlations with parameters of lipid profile were found among overall COPD patients, while in groups B and C – 13, in group D – 15.

Correlations between HDL and body mass index (BMI) (R = 0.69) as well as waist circumference (R = 0.58) in group B and inverse moderate relationship between level of reversibility of airflow obstruction and HDL (R = -0.62) and IA (R = -0.62) were found.

There is a strong positive correlation of CRP with TC (R = 0.80) and LDL (R = 0.95) in group C, which indicates an increase lipid involvement in the systemic inflammatory process in COPD. Besides there are positive correlations between TC, TG and SpO_2 (R = 0.57 and R = 0.64, respectively). Additionally, positive moderate relationship between TG and Tiffno's index (R = 0.56), TC and GFR (R = 0.62) was noted.

Positive moderate correlation between HDL and SpO_2 (R = 0.68), strong relationship between TG and IgE (R = 0.72), and negative strong correlation between TC and FVC (R = -0.70) were noted in group D. The peculiarity of this group is a large number of correlations which might be considered paradoxical. Positive correlations of TC (high) and CA (moderate) with Tiffno's index (R = 0.89 and R = 0.67, respectively), positive correlations of LDL (high) and VLDL (moderate) with GFR (R = 0.81 and R = 0.67, respectively) belong to them.

Analysis of correlation in COPD patients without comorbidity with CAD revealed high positive correlations of HDL with SpO_2 (R = 0.94) and reversibility of bronchial obstruction (R = 0.92).

The quantity of significant correlation relations increases with CAD comorbidity: relationship appears between TC and CRP (R = 0.498) which indicates the participation of lipids in systemic inflammation, and positive correlation between TC and Tiffno's index (R = 0.39) also appears.

6 significant correlations of various parameters with lipids were found in the COPD patients without CAD: positive relationship between TC and CRP (R = 0.75), GFR (R = 0.698), IgE (R = 0.61). There was a positive correlation of HDL with HbA_1C (R = 0.76). There was a positive strong relationship between LDL and GFR (R = 0.88), and moderate negative between VLDL and SpO_2 (R = -0.65).

The total number of correlations is retained at the comorbidity of COPD and AH. The relationship disappears between TC and CRP, IgE, besides relationship appears between HDL and waist circumference (R = 0.42), VLDL and HbA_1C (R = 0.499), HDL and GFR (R = 0.57), TC and the Tiffno's index (R = 0.42).

Consequently, lipids form a large quantity of correlations with various parameters of homeostasis at COPD such as CRP, Tiffno's index, reversibility of bronchial obstruction, SpO_2, IgE, HbA_1C. 75 correlation links with lipids were identified totally: there were identified 14 relations throughout group of COPD patients, 13 – in group B, 13 – in group C, 15 – in group D, 8 – in group of COPD with comorbidities of CAD, 4 – without CAD, 9 – in presence of AH as well as without AH. It should be noticed that the greatest number of interrelations were found with TC, LDL, VLDL and AI as a whole in COPD patients, only the link was detected with TG and no correlations with HDL. Comorbidity with CAD in COPD patients leads to an increase number of correlations in 2 times, which is not observed at worsening of COPD and comorbidity with AH. Namely, 5 relationships with TC, 4 correlations with pro-atherogenic lipoproteins, no relationship with HDL were found at comorbidity of COPD with CAD. Atherogenic fractions of lipids form 7 relationships with AH comorbidity, association with TC (3 links), LDL and VLDL (2 links), TG (2 links) and HDL (2 links) are presented in COPD patients without AH.

It should be noted that the variety and liability of correlation links, opposite direction, presence of relations, which are difficult to explain, and at glance, taking into account modern conception about the role and functions of lipids, these correlations seem to be paradoxical. Such correlations include a positive moderate association of TC with LDL (R = 0.41) and GFR (R = 0.40), a negative association between TC and waist circumference (R = -0.36) in overall COPD patients; out of 15 correlations 3 and might be considered as unexpected.

In addition, 3 out of 14 association revealed in group B are paradoxical, as follows, negative relationship between HDL and reversibility of bronchial obstruction (R = -0.62), positive association of HDL with BMI (R = 0.69) and waist circumference (R = 0.58).

Furthermore, 4 of the 13 correlations revealed in group C are paradoxical, so it is a positive correlation with GFR (R = 0.62), positive association of TC with TG (R = 0.57) and SpO_2 (R = 0.64), TG and Tiffno's index (R = 0.56).

Moreover, the greatest quantity of paradoxical links (6 out of 15, twice as many as in the other groups) was identified: between TC and the Tiffno's index estimated before and after treatment (R = 0.73 and R= 0.89, respectively), between TC and FEV_1 after treatment (R = 0.73), between LDL and GFR (R = 0.66), AI and Tiffno's index (R = 0.67). In addition, the correlation of TG with IgE (R = 0.72) appears precisely in this group. The level of TC was associated with IgE (R = 0.61) at comorbidity with AH and as well as correlation between HbA_1C and VLDL (R = 0.499).

Since the pathogenesis of comorbid states is currently considered in terms of systemic biology and general pathology as a change in universal network processes occurring at the genomic, molecular, and cellular levels we provide data about of correlations quantity in different subgroups of patients. Analyzing correlation relationships it is necessary to identify the most important and significant things in the informational flow and to look for parameters of order in it. A large number of paired associations can arise indirectly through other associations of concomitant diseases, and their number may increase exponentially with an increase in comorbidity [6]. Mistakes in evaluating the results of the study can also be associated with incorrect coding of diseases, inaccuracies in the collection of information, the effects of therapy, and, paradoxically, the

genetic factors themselves. Mathematical solutions are used in the network science to reduce the impact of indirect relationships between indicators; however, probabilistic relationships between diseases are not taken into account the complex system.

Metabolic networks, formed by groups of interacting proteins, carbohydrates, lipids, etc., are functioning together, coordinate and control the interrelated processes in the body. Networks are represented as a set of «nodes, hub», related oriented (enzyme – substrate, gene – protein, etc.) and undirected «ribs». There are distinguished the central nodes that have a greater number of connections, and peripheral, the number of connections which is much smaller.

The change in the activity of the central nodes contributes development of comorbid pathology. Complex biological systems acquire new (emergent) properties that cannot be explained due to particular diseases. Perhaps, these key positions in system biology and medicine may show the development of synthropies [3] and can explain the «paradox» correlations that were found in patients with COPD.

It is thought that synthropy is either a desire of living organisms to order the functioning of systems, organs, tissues, cells and to reduce entropy processes or a destruction, chaos, movement toward death. From this statement, the appearance of a large number of correlations, including paradoxical ones, in the group D with the 100 % comorbidity might be considered as manifestation of the synthropy. It is possible to regard such connections of the pulmonary function (PF) indicators with lipids as manifestations of adaptation in case of progressive hypoxia, hypoxemia, and hypercapnia through involvement in the maintenance of homeostasis of lipids, which stabilize cell membranes and are a source of energy.

New mathematical approaches arise in response to the emergence of «unsolvable tasks» in other fields of science and practice. These unsolvable tasks constitute the «no-knowledge card» that every scientist has and which is a priority for his research and linked to practical activities, the ability to manage processes.

Paradox correlations between different indicators (lipids, IgE and HbA_1C) are related to this «no-knowledge card» in our study. They also probably reflect the unknown processes of the organism adaptation to the organism's struggle with the severe, incurable disease through the involvement of lipids in this process.

The role of lipids in adaptive reactions is associated with the state of cell membranes structures under the pathology conditions that occurs when a system of protective, compensatory and restorative mechanisms is disrupted. Membrane adaptation is associated with changes in the composition of lipids and the functioning of transport systems.

Membrane adaptation is the basis of the ability to maintain adequate metabolic functions of organs and tissues. An important role is played by peroxidation syndrome of cell membranes [13] triggered by peroxisome proliferator-activated receptor (PPAR). PPAR relates to the central nodes of the metabolic network and causes the formation of a large number of connections with different homeostatic systems. The lipid matrix is considered as the most mobile structure of the metabolic network. The change in the phase state of the lipid matrix of biomembranes is determined their stability by damaging factors which go beyond the ranges of self-regulation, a pathological process develops. This determines the lipid strategy of biochemical adaptation to extreme effects; in particular, it is smoking and impact of other damaging environmental factors in case of COPD [14]. Possible clinical manifestations of such adaptation may be changes in the lipid spectrum, atherosclerosis, AH, gastrointestinal lesions, etc. Synthropic genes regulate phenotypes of clinical manifesttations in the case of synthropy.

Our study confirmed the involvement of lipids in systemic inflammation: correlations of TC with CRP in the group of patients with COPD ($R = 0.52$), group C ($R = 0.80$), in case of comorbidity with CAD ($R = 0.498$), in the group without AH ($R = 0.75$) were found.

It is possible to explain the results obtained by the impact of hypoxia on local and systemic inflammation, which increase systemic oxidative stress since PF in all patients declined. Active forms of oxygen start up processes of lipids and lipoproteins oxidation, accumulation of cholesterol, and enhance the systemic inflammatory response, the symptoms of which are presence of acute phase proteins, and especially CRP.

Unexpected correlations between lipids and IgE were found such as between TG and IgE ($R = 0.76$) in the D group and between TC and IgE ($R = 0.61$) in the group without AH.

Development of immediate type hypersensitivity reactions in patients with COPD is known and it is associated with sensitizing effects of tobacco smoke and environmental factors [15–16]. Pro-atherogenic properties of IgE are demonstrated in some studies [17–21]. The increase level of IgE in patients with unstable angina, dyslipidemia is established. It emphasizes the association of IgE with lipids and the instability of atherosclerotic plaque. Lipids correlate with the genes of basophils and mast cells; IgE accumulates in plaques and contributes to their increase. The opinion is expressed [21] that mast cells play a key role in the development of atherosclerosis and mastocytes secrete pro-atherogenic lipids in plaques.

These processes may not be accompanied with systemic manifestations, the total IgE level does not correlate with atherosclerosis progression. IgE functions in plaques causing accumulation of lipids, degradation of the matrix of the vascular wall and infiltration with pro-inflammatory immune cells. It is considered as key mechanisms of atherosclerosis development and pathogenesis of the plaque rupture.

The relationships between HDL and HbA_1C (R = 0.76) in the group of patients without AH and VLDL with HbA_1C (R = 0.499) in the group with AH were found. It confirms the relationship between lipid and carbohydrate metabolism in COPD patients. Among our patients 11 of them had type 2 DM, it is possible that synthropy of COPD with this disease not only CAD and AH might be present. The comorbidity of COPD and type 2 DM leads to severe COPD, frequent exacerbations, progressive reduction of ventilatory lung function as well as patient's life quality deterioration [22–25].

Cluster analysis of 12 indices (Fig. 1) including of lipid metabolism indices, CRP, anthropometric parameters (BMI), PFT indices (FEV_1, Tiffno's index) showed that HbA_1C forms a subcluster with TC. It also enters a cluster that includes a lipid spectrum, CRP and BMI on a large distance. Thus, HbA_1C is related closely to lipid metabolism, CRP and Tiffno's index forming COPD phenotype with metabolic syndrome (MS). FEV_1 and IgE form a separate cluster, so IgE might be the one of the markers of the eosinophilic phenotype of COPD.

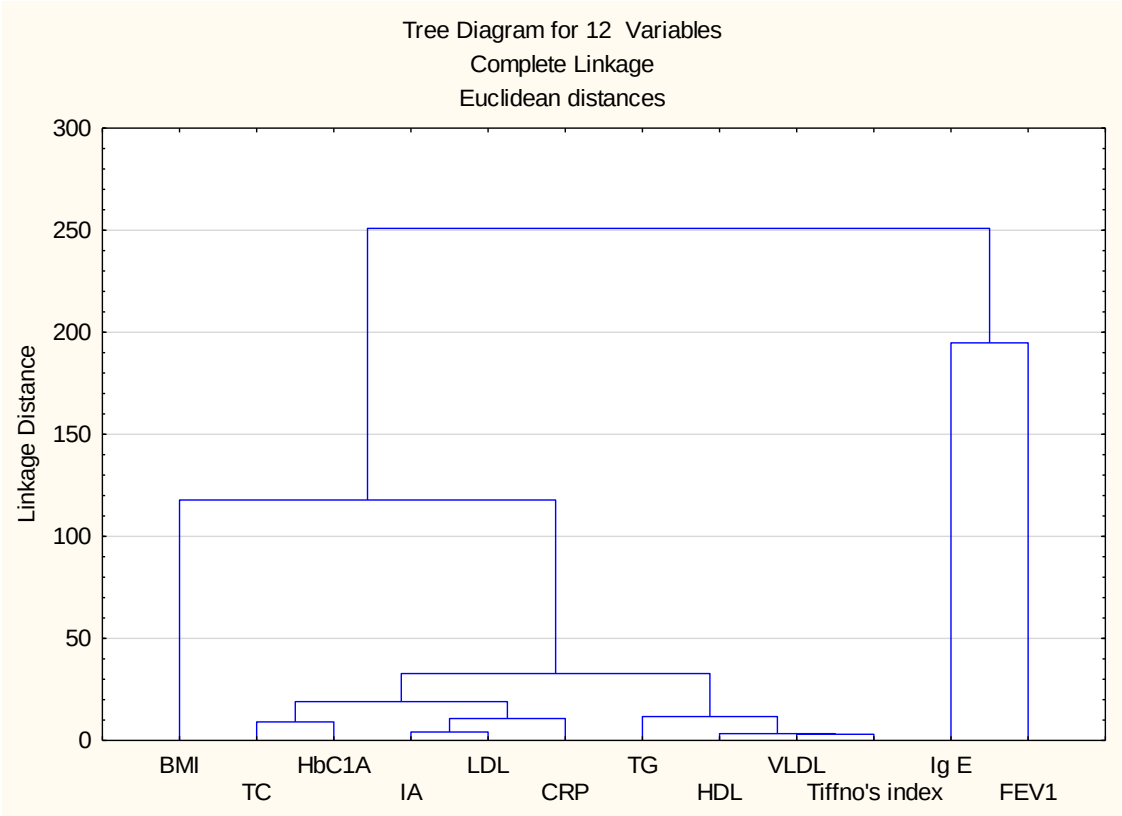

Fig. 1. Cluster analysis of lipid profile, systemic inflammation, pulmonary function and anthropometric data in patients with COPD with comorbid pathology

Investigation's results [25–29] of COPD comorbidity with MS are published. The opinion is suggested that MS (obesity, hypertension, atherogenic dyslipidemia, hyperglycemia, and insulin resistance) is predisposing factor in the development of systemic inflammation. Abdominal-visceral adipose tissue is considered as an active endocrine organ that supports a chronic systemic inflammatory process. Hypoxia due to COPD disrupts the balance between proinflammatory and anti-inflammatory factors in the large adipocytes zone, and activates the signaling pathways of inflammatory reactions [30]. Patients with MS and COPD have higher CRP and IL-6 levels, than patients without MS. The concentration of adiponectin inversely correlates with BMI in case of obesity. Adiponectin reduces insulin resistance by activating insulin in hepatocytes. Reduced level of adiponectin increases inflammation in the lung tissue. The severity of metabolic obesity should be assessed according to waist circumference. In our study, the correlations of lipid, waist circumference, BMI were unexpected: positive relationship between HDL (R = 0.69) and BMI (R = 0.58) and negative correlation between TC and WC (R = -0.36) were found. Perhaps this is due to the development of adaptation processes to the increase of BMI and waist circumference. According to the German investigation of MS, 50 % and 53 % of the COPD patients I and II stages, and 37 % and 44 % of the COPD patients III and IV stages have MS. According to Spanish study results obesity was noted in 25 % of COPD patients and violations of lipid metabolism were founded in 35 %. Among MS criteria, a lower frequency of central obesity and dyslipidemia was noted in patients with severe and extremely severe COPD: obesity was noted in 18 % of the total number of COPD patients, in 25 % of COPD patients with moderate severity of disease, and only in 6 % of COPD patients in severe stage of COPD [31]. The bronchial obstruction, dyspnea, acrocyanosis is more expressed in COPD patients with MS.

Among other things, the difficulty of the problem is nowadays that development of polypathy (comorbidity) is typical for patients with chronic multifactorial diseases. 80 % of elderly patients have 3 or more diseases, which are described as «involutional» [3]. According to the definition of entropy and synthropy [32, 2] life is an orderly and regular behavior of substance that based not only on the tendency of the transition from order to disorder, chaos, and death, but also to the constant maintenance of order and synthropy. Schrödinger [32] noted the amazing ability of the organism to concentrate on itself the «flow of order» avoiding the transition to atomic chaos associated with chromosomes. The organism produces entropy approaching death. This process is hampered by the metabolism that releases life from entropy and supports it through organization and ordering [33–34].

Nowadays, the concept of synthropy is widely used in medicine in the investigation of combined pathology, along with such related concepts as comorbidity, multimorbidity, and polypathy. This term means «mutual propensity, attraction of two diseases» as opposed to dystrophy – mutual repulsion. Despite this, there is [35–38] no clear understanding of synthropy, comorbidity, polypathy, polymorbidity. G. D. Fadeenko [39] considers the role of melatonin and nitric oxide metabolites in the pathogenesis of gastro-esophageal disease associated with COPD, and concludes that combined pathology is synonymous for synthropy. It seems relevant to use the term «polypathy» in general pathology, the term «comorbidity» in clinical practice and the allocation of «synthropy» as a genetically conditioned combination of several diseases. The terms of «multimorbidity», «polymerbidity» from the standpoint of genetics and epigenetics in the future also need to be clarified.

The chronic systemic inflammation, wherein an important role belongs to lipids, is a morphological basis of polypathy in COPD. Since there are several studies that confirm the presence of common gene alleles for COPD and CAD. The opinion that COPD and CAD are synthropy diseases could be accepted.

The diagnosis of a genetic disease caused by a group of synthropic genes and its characteristic clinical phenotypes (syndromes) by way of a syndrome of progressive irreversible bronchial obstruction, a syndrome of myocardial ischemia, AH syndrome, a syndrome of disturbed metabolism (carbohydrate, lipid, etc.) might be expected under the conditions of further genetic identification.

The analysis of the data shows the increasing correlations between different

indices of homeostasis with the progression of COPD in case of comorbidity. This indicates increasing of synthropy, attempts of homeostasis regulation, and search of adaptation ways to existence in conditions of severe illness.

The paradigm of reductionism was replaced by a network approach to studying the general laws and principles of human diseases. However, doctors often use polypragmazia treatment that is based on the reductionist approach [40].

The search for drugs, that are able to influence simultaneously all the links of the disturbed homeostasis, are currently underway based on the network model of the disease, the synthropy, the holistic approach to the problems of the disease [41–46]. It is proposed to use pleiotropic cholesterol-independent properties of statins as drugs such a group [41–46]. The basis of their effects is a decrease in the synthesis of intermediate cholesterol metabolism products, in particular, geranyl-geranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP). The anti-inflammatory effect of statins, their ability to change the properties of phagocytes, and subpopulations of T-lymphocytes were widely discussed. Cellular adhesion molecules have a moderate immunosuppressive effect. The anti-inflammatory effect of statins is accompanied with an increase in the content of antiatherogenic subfractions of LP, the cholesterol of pro-atherogenic subfractions decreases. There is evidence that statins reduce mortality from pulmonary insufficiency: a multivariate analysis of study results of statins effect in 7,700 COPD patients shows that the overall risk of death is reduced by 21 % and the risk of death from a lung dysfunction violation by 45 %. The American College of Chest Physicians does not recommend statins for prevention of COPD exacerbations. The prescription of statins for comorbidity of COPD is recognized as a matter of debate. According to the data [43, 46], exacerbations are less frequent and mortality decreases when statins are included in the complex therapy of COPD patients.

It is possible that further research of the problem of comorbidity and synthropy in COPD will open new paths to diagnosis, treatment and prevention this serious disease.

CONCLUSIONS

1. Increase of serum triglyceride level has been found among COPD and in combination with coronary artery disease and arterial hypertension. The other parameters of the lipid spectrum are within normal ranges.

2 Significant correlations between the content of C-reactive protein and lipid spectrum parameters indicate the involvement of lipids in systemic inflammation in COPD.

3. Correlations between the lipid spectrum and total IgE in the serum, which probably shows the role of immediate type hypersensitivity in the development of co-morbidity in COPD and atherosclerosis, were found.

4. Correlations between lipids, glycated hemoglobin, body mass index, and waist circumference can be signs of metabolic syndrome in COPD.

5. Cluster analysis of the homeostasis indices confirms the presence of similarity (affinity) between the parameters of the lipid spectrum, systemic inflammation, immediate type hypersensitivity, lung function in COPD patients.

6. A large number of differently directed correlation links between different indices of homeostasis in case of COPD that increases with progression of the disease, comorbidity with coronary artery disease, and may be a consequence of the processes of synthropy, adaptation, disadaptation of the organism under conditions of hypoxia. The study of the comorbidity problem, synthropy in COPD can open new approaches to diagnosis, treatment, prevention in the context of the concept of «integrative lung disease».

REFERENCES

1. Puzyrev V.P. Genetic Bases of Human Comorbidity. Genetika – Genetic 2015; 4: 491–495 (in Russ).
2. Vyatkin V.B. About application of the term «syntropy» in scientific research. Referativnyi zhurnal – Abstract journal 2016; 3: 81–84 (in Russ).
3. Shirinskiy V.S., Shirinskiy I.V. Comorbid diseases are animportant problem of the clinical medicine. Sibirskyi medicinskyi zhurnal – Siberian medical journal 2014; 29(1): 7–12 (in Russ).

4. Viliyasov V. B., Solovyeva N. V., Kremenitskaya S. A., Kuvshinova Y. V. Genetic syntropy or comorbidity? Clinical pathogenic analysis of the results of the patient study with monosomy 18p. The modern problem of the science and education. Elektronnyi naychnyi zhurnal – Electronic scientific journal 2017; 4: UPL; https: www.sciense-education.ru/ruarticle/view? id=26660 (in Russ).
5. Kutsenko M. A., Chuchalin A. G. Paradigm of the comorbidity: the COPD and IHD synthropy. Russkyimedicinskyizhurnal – Russian medical journal 2014; 22 (5): 389–392 (in Russ).
6. Marx P., Antal P., Bolgar B., Bagdy G., Deakin B., Juhazz G. Comorbidities in the diseasome are more apparent than real: what Bayesian filtering reveals about the comorbidities of depression. PLoS Comput Biol. 2017; 13 (6): e1005487.
7. Vanflettern L. E., Spruit M. F., Groenen M. Clusters of comorbidities based on validation objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am. J.Respir. Crit. Care Med. 2013; 187: 728–735.
8. Barabasi A. L. Network Medicine – from Obesity to the «Diseasome». N. Engl. J. Med. 2007; 357: 404–407.
9. Kalmikov O. O. Mechanisms of realisation of cardiorespiratory disturbanses in occupational diseases of bronchopulmonary system with accompanying coronary artery disease: diagnostic and prophylactic aspects. Dissertation synopsis for the degree of PhD, speciality 14.01.02 «Internal diseases», Kharkiv 2016; 40 p. (in Ukr).
10. Goh KI, Choi IG. Exploring the human diseasome: the human disease network. Briefings in Functional Genomics 2012; 11 (issue 6): 533–542.
11. COPD and Comorbidity. Ed. by Rabe KF, Wedzicha JA, Wouters EFM. European Respiratory Monograf 59, 2013; p.225.
12. Marshall VJ. Clinical biochemistry: translation from English. Edited by PhD Novikov NI – Moskov–St-Petersburg; 1999: 245–261 (in Russ).
13. Knyshova V. V, Gvozdenko T. A, Antonyuk M. V., Novgorodtseva T. P. Dyslipidemia phenotypes among patients with chronic disease of bronchopulmonary system. Bulletin phisiologii i patologii dikhaniya – Bulletin of physiology and breath pathology 2014; 51: 20–27 (in Russ).
14. Khristich T. N., Shestakova E. G., Teleki Ya. M., Gontsayruk D. A., Kushnir L. D. Comorbidity of the chronic obstructive pulmonary disease and coronary heart disease: peculiarities of pathogenic and management of patients (review of literature and own data). Ukrainskyi terapevticheskyi zhurnal – Ukrainian therapiutic journal 2013; 2: 101–108 (in Russ).
15. Slepchenko N., Mostovoy Y., Sidorov A. Is high level of IgE an additional problem in smoking patients with severe and very severe chronic obstructive pulmonare disease. Europ.Respir. Journ 2012; 40 (issue supple 56): 34–41.
16. Renkema T., Kerstjens H., Schouten J., Vonk J., Koster G., Postma D. The importance of serum IgE for level and longitudinal change in airways hyperresponsiveness in chronic obstructive pulmonare diseases. Clin. Exper. Allergy 1998; 28: 1210–1219.
17. Kukshekbaeva A. S., Nasonov E. L., Masab V. P. IgE in patients with ischemic heart disease. Klinicheskaya medicina – Clinical medicine 1990; 2: 36–38 (in Russ).
18. Korkmaz V. E., Oto A., Saraclar G., Oram E., Oram A., Ugurlu S.. Karamehmetoglu A., Karamehmetoglu E. Levels IgE in the serum of patients with coronary arterial disiese. Inf. J. Cardiol. 1991; 31: 199–204.
19. Wang J. Cheng X., Xiang MX. IgE stimulates human and mouse arterial cell apoptosis and cytokine expression and promotes atherosclerosis in Apoe mice. J. Clin. Inves. 2011; 121: 3564–3577.
20. Samaha H.MS. Total serum IgE in COPD patients. Egyptian Journ. of Chest Diseases and Tuberculosis 2015; 64 (Iss.3): 573–577.
21. Bot L., Shi G.P., Covanen P. Mast cells as effectors in atherosclerosis. Atheroscler. Thromb.Vasc. Biol. 2015; 35(2): 265–271.
22. Rana J., Mittelman M., Sheikh J., Hu F. COPD, astma and risk of type 2 diabetes in women. Diab etes care 2014; 27: 2478–2484.
23. Mannino D.M., Thorn D., Swensen A., Houlquin F. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007; 370: P. 765–773.
24. Titova E. A., Algasin A. I., Kornilova T. A. Features of the course of chronic pulmonary obstructive disease in patients with diabetes mellitus. Pulmonologiya – Pulmonology 2008; 5: 60–65 (in Russ)
25. Poulain M., Doucet M., Drapeua V. Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary diseases. Chron. Respir. Dis. 2008; 5: 35–41.
26. Ryazanov A. S., Kireev S. A., Eremenko N. N. Features chronic obstructive pulmonary disease clinical course in case of metabolic syndrome: the role of systemic inflammation. Ozhirenie i metabolism – Obesity and metabolism 2010; 2: 49–51 (in Russ).

27. Lin W. Y., Yao C. A., Wang H. C. Impaired lung function is associated with obesity and metabolic syndrome in adults. Obesity (Silver Spring) 2006; 14: 1654–1661.
28. Marquis K., Maltais F., Duquay V. The metabolic syndrome in patient with chronic obstructive pulmonary disease. J. Cardiopulm. Rheabil. 2005; 25: 226–232.
29. Park S. K., Larson J. L. Metabolic syndrome and associated factors in people with Chronic Obstructive Pulmonary Disease. Western Journal of Nursing Research. 2014; 36(5): 620–642.
30. Eisner MD, Blanc PD, Sidney S. Body composition and functional limitation in chronic obstructive pulmonaire disease. Respir. Res. 2000; 7: 1–10.
31. Steuten L.M., Creutzberg E.C., Vrijoef H.J., Wonters F.F. COPD as a multicomponent disease: Inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. Prim. Care Respir. J. 2006; 15: 84–91.
32. Shredinger E. What is life from the physics perspectives? Translation from English by Malinovskyi A. A., Moscow, RIMIS 2009; 176 (in Russ).
33. Malinetskii G. G. Theory of self-organization. On the cusp of IV paradigm. Komputerniye issledovaniya i modelirovanie – Computer research and modeling 2013; 3: 315–366 (in Russ).
34. Chernavskyi D. S. Synergetics and information (dynamic information theory). 2nd edition, UPSS 2017; 304 (in Russ).
35. von Seht L. Weiteres uber Syntropie kindlicher Krankheitszustande. Zeitschrift fur Kinderheilkunde 1922; 31(issue 5): 208–213.
36. van Eeden S. Leipsi S. J. The relationship between lung inflammation and cardiovascular disiese. Am.J. Respir. Crit.CareMed. 2012; 186 (1): 11–16.
37. Sin D. D, Man S. F. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc. Am. Thorac. Soc. 2005; 2 (1): 8–11.
38. van den Akken M., Buntix T., Roos S., Knottnerus J. A. Comorbidity or multimorbidity: what is a name? A review of literature. Eur. J. Gen. Pract.1996; 2(2): 65–70.
39. Fadieienko G. D., Kamenir V. M. Relationship of melatonin metabolites and nitric oxide in pathogenesis of gastroesophageal reflux disease in combination with chronic obstructive pulmonary disease. Ukrainskyi terapevticheskyi zhurnal – Ukrainian therapiutic journal 2009; 4: 78–87 (in Russ).
40. Wong C. Y., Chandry S. I., Desai M. M. Trends in comorbidity, disability, and polypharmacy in heart failure. Am. J. Med. 2011; 124: 136–143.
41. Shirinskiy V. S., Shirinskiy I. V. Hub therapy as a new opportunity for treatment of comorbid diseases. Sibirskyi medicinskyi zhurnal – Siberian medical journal 2014; 29(4): 13–21 (in Russ).
42. Gerasimova EB, Bazdyrev ED, Smakotina SA, Hryachkova ON, Soldatova NV. Efficiency of hypolipidemic therapy at patients with chronic obstructive pulmonary disease. Medicina i obrasovanie v Sibiri – Medicine and education in Sibiria 2014; 2: http://ngmu.ru/cozo/mos/article/text_full.php?id=1304 (in Russ).
43. Lahousse L, Loth D, Joos G. Statins, systemic inflammation and risk of death in chronic obstructive pulmonary disease: the Rotterdame study. Pulm. Pharmacol. Ther. 2013; 26: 212–217.
44. Liao H. K., Laufs U. Pleotropic effects of statin. Ann.Rev. Pharmacol.Toxic. 2005; 45: 89–118.
45. Tandon V., Bano G., Khagjuria V. Pleotropic effects of statins. Indian J. Pharmacol. 2005; 2 (37): 77–85.
46. Yong R. P., Hopkins R., Eaton T. E. Pharmacological actions of statins: potential utility in COPD. Eur. Respir. Rev. 2009; 18: 1–11.

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FIBROTIC CHANGES IN PATIENTS WITH CHRONIC HEART FAILURE WITH CARDIAC DYSSYNCHRONY AND ASSOCIATED TYPE 2 DIABETES MELLITUS

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The study of fibrosis markers was carried out on 72 observed patients (mean age (69 ± 10.37) years) with chronic heart failure (CHF) of ischemic genesis with manifestations of cardiac dyssynchrony (CD) and concomitant type 2 diabetes mellitus – Galectin 3 and matrix metalloproteinase 1. All patients were divided into 2 groups, depending on the presence of CD. The CD was evaluated according to a conventional technique, the volume fraction of interstitial collagen was measured using the formula of J. Shirani and co-authors, the levels of Galectin-3 and matrix metalloproteinase 1 – by the enzyme-linked immunoassay according to the manufacturer's instructions. The data were processed using parametric and nonparametric statistics. It was revealed that the level of fibrosis development was higher in the group of patients with CD than in the group without CD. This indicates the dependence of the development of myocardial sites asynchronous reduction with the presence of interstitial collagen development. That further requires the study of the effect of anti-fibrotic, anti-ischemic and hypoglycemic agents on the progression of CD to prevent subsequent myocardial remodeling.

KEY WORDS: volume fraction of interstitial collagen, chronic heart failure, cardiac dyssynchrony, Galectin 3, matrix metalloproteinase 1

ФІБРОТИЧНІ ЗМІНИ У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ З ДИССИНХРОНІЄЮ МІОКРАДА ТА СУПУТНІМ ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ

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У 72 обстежуваних (середній вік (69 ± 10,37) років) з хронічною серцевою недостатністю (ХСН) ішемічного генезу з проявами диссинхронії міокарда (ДМ) та супутнім цукровим діабетом 2-го типу проведено вивчення маркерів фіброзу: Галектину 3 та матриксної металопротеїнази 1. Всі пацієнти розділені на 2 групи в залежності від наявності ДМ. ДМ оцінювали за загальноприйнятою методикою, об'ємну фракцію інтерстиціального колагену вимірювали за допомогою формули J. Shirani і співавторів, рівень Галектіна-3 і матриксної металопротеїнази 1 за допомогою імуноферментного методу згідно з інструкцією від виробника. Дані обробляли методами параметричної та непараметричної статистики. Виявлено, що в групі хворих з ДМ рівень розвитку фіброзу був вищим за рівень у групі без ДМ. Це вказує на залежність розвитку асинхронного скорочення ділянок міокарда з наявністю розвитку інтерстиціального колагену, що в подальшому потребує вивчення дії противофібротичних, антиішемічних та гіпоглікемічних засобів на прогресування ДМ для запобігання у подальшому ре моделювання міокарда.

КЛЮЧОВІ СЛОВА: об'ємна фракція інтерстиціального колагену, хронічна серцева недостатність, диссинхронія міокарда, Галектин 3, матриксна металопротеіназа 1

ФИБРОТИЧЕСКИЕ ИЗМЕНЕНИЯ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ С ДИССИНХРОНИЕЙ МИОКРАДА И СОПУТСТВУЮЩИМ САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

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У 72 обследуемых (средний возраст (69 ± 10,37) лет) с хронической сердечной недостаточностью (ХСН) ишемического генеза с проявлениями диссинхронии миокарда (ДМ) и сопутствующим сахарным диабетом 2-го типа проведено изучение маркеров фиброза: Галектина 3 и матриксной

металлопротеиназы 1. Все пациенты разделены на 2 группы в зависимости от наличия ДМ. ДМ оценивали по общепринятой методике, объемную фракцию интерстициального коллагена измеряли с помощью формулы J. Shirani и соавторов, уровень Галектина-3 и матриксной металлопротеиназы 1 с помощью иммуноферментного метода согласно инструкции от производителя. Данные обрабатывали методами параметрической и непараметрической статистики. Выявлено, что в группе больных с ДМ уровень развития фиброза был выше уровня в группе без ДМ. Это указывает на зависимость развития асинхронного сокращения участков миокарда с наличием развития интерстициального коллагена, что в дальнейшем требует изучения действия противофибротических, антиишемических и гипогликемических средств на прогрессирование ДМ для предотвращения последующего ремоделирования миокарда.

КЛЮЧЕВЫЕ СЛОВА: объемная фракция интерстициального коллагена, хроническая сердечная недостаточность, диссинхрония миокарда, Галектин 3, матриксная металлопротеиназа 1

INTRODUCTION

Excessive accumulation of fibrosis has pathological effects on the diastolic function of the myocardium [1]. The number of focal collagen fibers increases in patients with type 2 diabetes mellitus (DM) before the increasing of the total collagen content, that leads to a decrease in myocardial capacity, which is due to glycation of collagen fibers and, as a result, an increase in the weight of the myocardium. Hypertrophy of cardiomyocytes in patients with diabetic cardiomyopathy has been studied for a long time, but its contribution to the ventricular hypertrophy hasn't still been understood completely [1–2]. Detection of new biomarkers of subclinical damage can improve the assessment of the risk of cardiovascular complications. It is becoming relevant to study the fibrosis markers for timely diagnosis of primary changes of extracellular matrix in patients with type 2 DM. Among the manifestations of cardiovascular disease, the main attention is paid to chronic heart failure (CHF) due to the high prevalence of this syndrome, which is associated with an increased risk of mortality among populations throughout the world. There is evidence that plasma levels of galectin (Gal)-3 correlate with the prevalence of type 2 DM and associated metabolic conditions, suggesting that the pharmacological blockage of this lectin can be successful in treating CHF in patients with diabetes [3–4].

The work was carried out according to the plan of research works of the Department of Therapy and Nephrology of the Kharkiv Medical Academy of Postgraduate Education «Optimization of the treatment of chronic heart failure» (SR No. 0117U000585).

OBJECTIVE

To study the features of changes in fibrosis markers – galactine-3 and matrix metalloproteinase-1 in patients with CHF with CD manifestations and associated type 2 DM.

MATERIALS AND METHODS

Complex examination of 72 patients with comorbid pathology – CHF of ischemic origin and type 2 DM was carried out. All patients were on treatment in the therapeutic and cardiology department at Kharkiv City clinical hospital of urgent and emergency aid named after Prof. O. I. Meshhaninov.

Patients were with known CHF, New York Heart Association (NYHA) class I-IV and left ventricular ejection fraction (LVEF) of ≥ 45 % («average» or «preserved» according to the criteria of the European Society of Cardiology, 2016) [5]. The average age of patients was (67.45 ± 10.32) years. Type 2 DM was diagnosed according to the criteria of the American Diabetes Association and the American Diabetes Association Diabetes Care, 2017, and European Association for the Study of Diabetes (EASD). CD was diagnosed according to the recommendations of the European Association of Echocardiography [5–6]. CD was divided into intraventricular, interventricular, atrioventricular and combined.

Instrumental methods – echocardiography with determination of CD indices and electrocardiography (ECG) were performed on all patients with CHF of ischemic genesis and type 2 DM.

The evaluation of myocardial fibrosis was performed with the determination of the content of Gal-3 and matrix metalloproteinase (MMP) 1 in serum using the immune-enzyme method. Galectin-3 was evaluated using Human Galectin-3 kit (Platinum ELISA; eBioscience,

Bender MedSystems, Austria) and MMP-1 content – using the «Human MBZ-1» kit (ELISA, Abfrontier Biotechnology supplier, South Korea).

The volume fraction of interstitial collagen (ICVF) was calculated according to the method, which was determined based on the total voltage of the QRS complex in 12 standard leads, growth, myocardial mass of the left ventricle (LVMM), where the normal level is 1–2 % [7].

ICVF = (1–1,3 * ((total QRS * height) / LVMM)) * 100. Where ICVF is an interstitial collagen volume fraction, %; LVMM – left ventricle myocardial mass, g; height, m; total QRS volt, mm.

To perform the task, the subjects under study (n = 72) were divided into 2 groups. Group 1 (n = 56) with CD and group 2 (n = 16) without CD.

The statistical processing of the obtained results was performed on a personal computer using Microsoft Office Excel 2007 and STATISTICA 6.0. To determine the continuous scale, the mean sample and median were used as indicators of the central trend, the data are presented in the results of the study, as M ± m, where M is the arithmetic mean, m is the mean square (arithmetic) deviation; interquartile range, minimum and maximum value – as measures of spread. The discrepancy was considered reliable if the probability of random difference did not exceed 0.05 ($p < 0,05$).

RESULTS AND DISCUSSION

The mean content of Gal-3 in the studied patients was (7.19 + 0.48) ng/ml, MMP-1 (0.58 + 0.19) ng/ml, and ICVF was (7.22 ± 0.29) %.

Patients were divided into 2 groups to determine the levels of fibroblasts regarding the presence of CD: 1st group included 56 people with DM; 2nd group was represented by 16 persons without signs of DM (Table).

Table 1

The activity of fibrosis markers in patients with type 2 diabetes and CHF of ischemic genesis, depending on the presence of CD (M + m)

Indicator	CD (n = 56)	Without CD (n = 16)
Gal-3, ng/ml	7,49 + 0,6	6,14 + 0,42
MMP-1, ng/ml	0,46 + 0,2	1 + 0,47*
ICVF, %	7,6 ± 4,03	6,52 ± 2,36

**Notes: – the degree of differences probability of in group 2 compared to group 1 ($p < 0,05$)*

The obtained results indicate that the formation of CD leads to an increase in the expressiveness of fibrotic changes. The dependence of levels of fibrosis markers on the degree of development of CD was investigated. The growth of the Gal-3 levels was observed under the condition of the presence of combined CD forms.

Thus, the level of Gal-3 was the highest in patients with simultaneous combination of intraventricular, interventricular or atrioventricular CD (n = 28), while in isolated forms of CD, that is in the presence of one of the forms, the content of Gal-3 was significantly smaller (Fig.). The content of MMP-1 also depended on the combination of CD and was the smallest in patients with combined (n = 28) CD forms. The size of the ICVF also correlated with the forms of CD (Fig.).

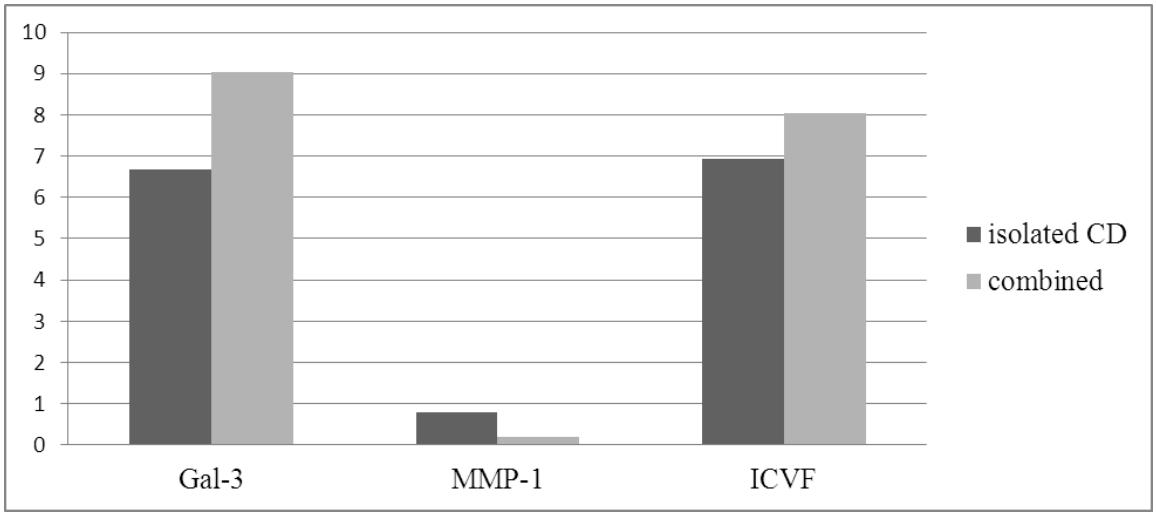

Fig. The activity of fibrosis indicators in patients with CD against the background of CHF

CONCLUSIONS

When type 2 DM combined with CHF of the ischemic genes, the Gal-3 serum level increases, that correlates with the progression of the mechanical CD leading to the myocardial rejuvenation. Content of MMP-1 depends on the form of mechanical CD – decreasing in combined forms.

PROSPECTS FOR FUTURE STUDIES

It remains relevant to further explore the characteristics of changes in the fibrosis markers, depending on the use of hypoglycemic and anti-ischemic therapy, and its effect on CD.

REFERENCES

1. Rudenko T. A. Role of glycaemia level in the development of interstitial collagen in patients with coronary heart disease and type 2 diabetes / T. A. Rudenko // The Journal of V. N. Karazin Kharkiv National University, series Medicine. – 2015. – No. 30. – p. 30–33.
2. Ozturk D. Association between serum galectin-3 levels and coronary atherosclerosis and plaque burden/structure in patients with type 2 diabetes mellitus / D. Ozturk, O. Celik, S. Satilmis, et al. // Coronary artery disease. – 2015. – Vol. 26. – No. 5. – p. 396–401.
3. Cuspidi C. Galectin-3 and Hypertensive Heart Disease / C. Cuspidi, M. Tadic, C. Sala // The Journal of Clinical Hypertension. – 2016. – Vol. 18. – No. 6. – p. 503–505.
4. Tan K. C. B. Galectin-3 is independently associated with progression of nephropathy in type 2 diabetes mellitus / K. C. B. Tan, C. L. Cheung, A. C. H. Lee // Diabetologia. – 2018. – p. 1–8.
5. Atherton J. J., Bauersachs J. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. – Web Addenda. – 2016.
6. Gorcsan J. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting–a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society / J. Gorcsan, T. Abraham, D. A. Agler // Journal of the American Society of Echocardiography. – 2008. – Vol. 21. – No. 3. – p. 191–213.
7. Shirani J. Usefulness of the Electrocar diagram and Echocar diagram in predictingtheamount of inter stitialmyocardialcjllagen in endomyocardial biopsy specimens of patients with chronic heart failure / J. Shirani, R. Pick, Y. Quo // Am. J. Cardiol. – 1992. – Vol. 69. – P.1502.

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THE FREQUENCY OF USE OF COMBINATIONS OF ANTIHYPERTENSIVE DRUGS IN PATIENTS WITH DIFFICULT-TO-CONTROL HYPERTENSION ON THE BACKGROUND OF BIOFEEDBACK AND PACED BREATHING AND HEART RATE VARIABILITY

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The frequency of administration of combinations of antihypertensive drugs and its changes at different stages of observation was studied in 60 patients with difficult-to-control arterial hypertension (DTCAH) (32 men and 28 women) aged 59.0 ± 9.4. All patients were randomly divided into two subgroups: biofeedback (BFB) in the loop of paced breathing (PB) and heart rate variability (HRV) (33 patients) – basic subgroup, subgroup of comparisons (27 patients). Determined that patients with DTCAH in the subgroup of patients with the BFB in the loop of PB there has been a reduction of four-component antihypertensive therapy to three-component and in the subgroup of comparisons the frequency of the appointment of a four-component therapy was increased. At the same time, it was found that the addition of drug therapy with regular BFB sessions in the loop of PB contributed to the potentiation of the antihypertensive effect in patients with DTCAH. It is concluded that the BFB in the loop of PB and HRV can be used as a technology to improve the efficiency of control of blood pressure in patients with DTCAH.

KEY WORDS: difficult-to-control arterial hypertension, heart rate variability, biofeedback, paced breathing

ЧАСТОТА ПРИЗНАЧЕННЯ КОМБІНАЦІЙ АНТИГІПЕРТЕНЗИВНИХ ПРЕПАРАТІВ У ПАЦІЄНТІВ З ВАЖКО КОНТРОЛЬОВАНОЮ АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ НА ТЛІ ПРОВЕДЕННЯ СЕАНСІВ БІОЛОГІЧНОГО ЗВОРОТНОГО ЗВ'ЯЗКУ В КОНТУРІ МЕТРОНОМИЗИРОВАННОГО ДИХАННЯ

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Вивчено частоту призначення комбінацій антигіпертензивних препаратів та її зміни на різних етапах спостереження у 60 пацієнтів з важкоконтрольованою артеріальною гіпертензією (ВАГ) (32 чоловіки та 28 жінок) у віці 59,0 ± 9,4. Всі пацієнти випадковим чином були розділені на дві підгрупи: з біологічним зворотним зв'язком (БЗЗ) в контурі метрономізованного дихання (МД) (33 пацієнтів) – основна підгрупа та підгрупа порівняння (27 пацієнтів). Встановлено, що у пацієнтів з ВАГ у підгрупі пацієнтів з БЗЗ в контурі МД зазначається скорочення чотирикомпонентниї антигіпертензивної терапії до трикомпонентної, а в підгрупі порівняння зростає частота призначення чотирьохкомпонентної терапії. При цьому встановлено, що доповнення медикаментозної терапії регулярними сеансами БОС в контурі МД сприяє потенціювання антигіпертензивного ефекту у пацієнтів з ВАГ. Робиться висновок, що БЗЗ в контурі МД під контролем параметрів варіабельності серцевого ритму (ВСР) може бути використана як технологія підвищення ефективності контролю артеріального тиску при ВАГ.

КЛЮЧОВІ СЛОВА: важко контрольована артеріальна гіпертензія, варіабельність серцевого ритму, біологічний зворотний зв'язок, метрономізоване дихання

ЧАСТОТА НАЗНАЧЕНИЯ КОМБИНАЦИЙ АНТИГИПЕРТЕНЗИВНЫХ ПРЕПАРАТОВ У ПАЦИЕНТОВ С ТРУДНОКОНТРОЛИРУЕМОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ НА ФОНЕ ПРОВЕДЕНИЯ СЕАНСОВ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В КОНТУРЕ МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ

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Изучена частота назначения комбинаций антигипертензивных препаратов и ее изменения на различных этапах наблюдения у 60 пациентов с трудноконтролируемой артериальной гипертензией (ТАГ) (32 мужчины и 28 женщин) в возрасте 59,0 ± 9,4. Все пациенты случайным образом были разделены на две подгруппы: с биологической обратной связью (БОС) в контуре метрономизированного дыхания (МД) и вариабельности сердечного ритма (ВСР) (33 пациентов) – основная подгруппа, подгруппа сравнения (27 пациентов). Установлено, что у пациентов с ТАГ в подгруппе пациентов с БОС в контуре МД отмечается сокращение четырехкомпонентной антигипертензивной терапии до трехкомпонентной, а в подгруппе сравнения возрастает частота назначения четырехкомпонентной терапии. При этом установлено, что дополнение медикаментозной терапии регулярными сеансами БОС в контуре МД способствует потенцированию антигипертензивного эффекта у пациентов с ТАГ. Делается вывод, что БОС в контуре МД под контролем параметров ВСР может быть использована как технология повышения эффективности контроля АД при ТАГ.

КЛЮЧЕВЫЕ СЛОВА: трудноконтролируемая артериальная гипертензия, вариабельность сердечного ритма, биологическая обратная связь, метрономизированное дыхание

INTRODUCTION

Currently, treatment of difficult-to-control arterial hypertension (DTCAH) is an important problem due to the widespread prevalence of patients with DTCAH (30.4–31.8 % of the total population of patients with hypertension) [1], rapid progression of target organ damage and a high risk of cardiovascular events [2].

DTCAH is characterized by the inability to achieve target blood pressure values, despite the appointment of three or more antihypertensive drugs, including diuretics [3]. Due to the absence of randomized clinical trials, the selection of therapy for persons with TAG occurs empirically, taking into account national recommendations for the treatment of hypertension [4]. The best treatment strategy in this case is to select a combination of antihypertensive drugs, which will affect the various links of pathogenesis and physiological mechanisms of hypertension, as well as take into account the comorbidity of a particular patient.

OBJECTIVE

The aim of the work is to study the change in the frequency of prescribing combinations of antihypertensive drugs used in patients with DTCAH on the background of biofeedback (BFB) in loop of heart rate variability (HRV) and paced breathing (PB).

MATERIALS AND METHODS

On the clinical base of the Kharkov city outpatient clinic No. 24 and the State Institution «Kharkov Clinical Hospital for Railway Transport No. 1» 60 patients with DTCAH were examined (32 men and 28 women). Average age is 59,0 ± 9,4 years. All patients were ran-domly divided into two subgroups: with BFB in the loop of paced breathing (33 patients) – basic subgroup, subgroup of comparisons (27 patients).

The inclusion criteria in the study were any stage and degree of arterial hypertension (AH). The criterion of DTCAH was the presence of a persistent increase in BP above the target level, despite the simultaneous use of three or more antihypertensive drugs of various classes in adequate therapeutic doses, including a diuretic.

Exclusion criteria were heart failure functional class IV, acute coronary syndrome, rhythm and conduction disorders, diabetes mellitus, chronic respiratory insufficiency, bronchial asthma, chronic obstructive pulmonary diseases, peptic ulcer and duodenal ulcer at the stage of exacerbation, systemic diseases of connective tissue, tumors.

Drug therapy was carried out according to the Ukrainian recommendations on the management of patients with AH [4]. Taking into account the degree of severity of

hypertension, the presence of target organ damage and concomitant pathology in patients with DTCAH one of the following combinations of antihypertensive drugs was prescribed: Inhibitor of angiotensin converting enzyme (ACE)/blockers of the renin-angiotensin-aldosterone system (RAAS) + calcium channel blocker (CCB) + diuretic; ACE inhibitor/blocker of the RAAS + CCB + diuretic + antagonist of mineralocorticoids; Beta-blocker + ACE inhibitor/blocker of the RAAS + CCB + diuretic; ACE inhibitor/blocker of the RAAS + CCB + diuretics + hypotensive drugs of the central action.

BFB was carried out on the computer diagnostic complex CardioLab 2009 («HAI-Medica», Ukraine) with the module «Biofeedback», including software-related visual-sonic metronome breathing and dynamic algorithm for determining the current values of HRV parameters, changing under the influence of PB. The breathing rate was set by the «Biofeedback» software module.

Statistical processing was carried out using Microsoft Excel. Qualitative variables described by relative values were used for statistical evaluation of the results: % and their deviation – σ. The accuracy of differences between groups is determined by the parametric Student's T-test. The expected result was determined by the level of reliability $p < 0.05$.

RESULTS AND DISCUSSION

In table 1 the frequency of prescribing combinations of antihypertensive drugs used in patients with DTCAH in the subgroup of patients with BFB in the loop of PB and the subgroup of comparison at the observation stages – 3, 6 months and a year is presented.

Table 1

Frequency of administration of antihypertensive drug combinations in patients with difficult-to-control hypertension during treatment (% ± σ)

Combinations of antihypertensive drug	Subgroups of patients							
	Patients with BFB in the loop of PB				Comparison subgroup (BFB without PB)			
	Stages of therapy							
	Before treatment	3 month	6 month	1 year	Before treatment	3 month	6 month	1 year
ACE inhibitor/blocker of the RAAS + CCB + diuretic (% ± σ)	39,5 ± 4*	44,3 ± 5	46,3 ± 4	45,5 ± 3	42,4 ± 5**	28,3 ± 6	25,3 ± 2	19,2 ± 4
ACE inhibitor/blocker of the RAAS + CCB + diuretic + antagonist of mineralocorticoids (% ± σ)	33,3 ± 3 *	33,3 ± 3	34,3 ± 4	36 ± 4	21 ± 3**	45 ± 3	48 ± 5	50 ± 4
Beta-blocker + ACE inhibitor/blocker of the RAAS + CCB + diuretic (% ± σ)	24,2 ± 3*	20,6 ± 3	19,4 ± 2	18,5 ± 2	34,6 ± 4 **	21,1 ± 3	18,4 ± 5	20 ± 3
ACE inhibitor/blocker of the RAAS + CCB + diuretics + hypotensive drugs of the central action (% ± σ)	3 ± 2*	1,8 ± 2	0 ± 0	0 ± 0	2 ± 1**	5,6 ± 3	8,3 ± 4	10,8 ± 3

Both groups of patients before the beginning of the séances were dominated by the administration of a combination ACE inhibitor/blocker of the RAAS + CCB + diuretic. In the subgroup of patients with BFB in the loop of PB combinations of ACE inhibitor/blocker of the RAAS + CCB + diuretic + antagonist of mineralocorticoids, beta-blocker + ACE inhibitor/blocker of the RAAS + CCB + diuretic, ACE inhibitor/blocker of the RAAS + CCB + diuretic + hypotensive drugs of the central action were less frequently prescribed. The ratio of prescription of these combinations of drugs in the subgroup with

BFB in the loop of PB was 13:11:8:1, at the stage of 3 month observation – 24,6:18,5:11,4:1, at the stage of 6 month observation – 3:5,7:1,8:1 and at the stage of annual observation this ratio was 2,5:1,9:1: 0. This indicates that the dominance of the assignment of combination ACE inhibitor/blocker of the RAAS + CCB + diuretic was preserved, and also it was noted the declining trend in antihypertensive therapy from four-component to three-component. Frequency of assignment combination which includes beta-blocker + ACE inhibitor/blocker of the RAAS + CCB + diuretic decreased in 1,3 times. Combination of ACE inhibitor/blocker of the RAAS + CCB + diuretic + hypotensive drugs of the central action at the annual stage of treatment wasn't use.

In the subgroup of comparison, the initial ratio of combinations of antihypertensive drugs changed from 21,2:10,5:17,3:1 to 5:8:4.8:1 at the three – month stage, 7:4,6:2,2:1-at the semi-annual stage and by the end of the year of observation it was 1,7:4,6:1,8:1. At the annual stage of therapy, the predominant combination was a combination of ACE inhibitor/RAAS blocker + BCC + diuretic + mineralocorticoid antagonist, the frequency of administration increased by 2,4 times. There was also an increase of administration of combination ACE inhibitor/blocker of the RAAS + CCB + diuretics + anti-hypertensive drugs of central action (in 5,4 times). On the contrary, the frequency of administration of combination ACE inhibitor/RAAS blocker + BKK + diuretic decreased by 2,2 times, which demonstrates the predominance of four-component antihypertensive therapy at the annual stage in patients with DTCAH without PB.

The obtained results , according to which the addition of drug therapy with BFB in the loop of PB allows achieving better blood pressure control in patients with DTCAH, are in accordance with the data in patients with controlled AH [5–7]. However, publications on the effectiveness of BFB in the loop of PB in patients with DTCAH, are absent in the literature.

Our observations confirm the need for combined antihypertensive therapy in patients with DTCAH. The addition of drug therapy by regular BFB sessions in the loop of PB has an additional effect on the neurohumoral regulation, which contributes to the potentiation of the antihypertensive effect.

The results show that the addition of antihypertensive therapy by BFB in the loop of HRV and PB reduces the number of prescribed drugs.

CONCLUSIONS

1. The addition of drug therapy with regular BFB sessions in the loop of PB contributes to the potentiation of the antihypertensive effect in patients with DTCAH.

2. There is reduction of four-component antihypertensive therapy to three-component in the subgroup of patients with BFB in the loop of PB. On the contrary in the comparison subgroup the frequency of administration of four-component therapy increases.

3. BFB in the loop of HRV and PB control can be used as a technology to improve the effectiveness of control blood pressure in patients with DTCAH.

PROSPECTS FOR FURTHER RESEARCHES

In the future, it seems appropriate to study the dynamics of parameters of BFB and blood pressure in patients with the DTCAH at various stages of treatment.

REFERENCES

1. Systolic and diastolic short-term blood pressure variability and its determinants in patients with controlled and uncontrolled hypertension: A retrospective cohort study / Martino F. Pengo, Giacomo Rossitto, Valeria Bisogni [et. al.] // Blood Pressure –2015. – No. 24 (2). – P. 124–129.
2. Muntner P, Davis BR, Cushman WC, Bangalore S, Calhoun DA, Pressel SL, et al. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). Hypertension (2014) 64:1012–21.
3. ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) / Giuseppe Mancia, Robert Fagard, Krzysztof Narkiewicz [et al.]. // Journal of Hypertension. – 2013. – No. 31. – P. 1281–1187.

4. Unifikovaniy klinichniy protokol pervinnoyi, ekstrennoyi ta vtorinnoyi (spetsializovannoyi) dopomogi «Arterialna gipertenziya». – Praktichniy likar. – 2013. – No. 2. – stor.43–51).
5. Kulik A. L. Biofeedback and modern clinical practice. / A. L. Kulik, N. I. Yabluchanskiy // The Journal of V. N. Karazin Kharkiv National University. Series «Medicine». – 2011. – No. 22 (975). – P. 82–93.
6. Shmidt E. Yu. Closed loop biofeedback of heart rate variability and paced breathing efficacy evaluation in patients with arterial hypertension / E. Yu. Shmidt, A. L. Kulik, A. V. Martyinenko [et al.] // The Journal of V. N. Karazin Kharkiv National University. Series «Medicine». – 2011. – No. 22 (975). – P. 63–67.
7. Belal S. A. S. The influence of biofeedback sessions in closed loop of heart rate variability and paced breathing on systolic blood pressure control during standart drug therapy in patients with arterial hypertension / S. A. S. Belal, N. A. Vodyanitskaya, M. I. Yabluchanskiy // The Journal of V. N. Karazin Kharkiv National University. Series «Medicine». – 2015. – No. 29. – P. 11–21.

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THE PROPORTION OF PATIENTS WITH HYPERTENSION IN THE GROUPS OF TERMS PROLONGED QTc INTERVALS PER DAY DATA OF AMBULATORY ECG MONITORING IN DEPENDENCE FROM CLINICAL SIGNS

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The study of the proportion of patients in 82 patients with hypertension in groups of different periods of prolonged QTc per day was performed based on the data of the AM of the ECG, depending on the clinical signs. Depending on the duration of prolonged QTc per day, the patients were assigned to one of three groups: group 1 – the term extended by day of the interval QTc from 0 to 33.3 %, group 2 – from 33.4 to 66.6 %, group 3 – from 66.6 to 100 %. The proportion of patients with hypertension was determined in the groups of the prolonged QTc interval depending on age, sex, weight of patients, type of circadian heart rate index, stage, degree and prescription of EH, presence of coronary heart disease, FC and stage of CHF and diabetes mellitus. According to the AM ECG, an prolonged QTc interval occurs in each patient with hypertension, with an increase of 0 to 33.3 % per day, it is detected in 76 %, from 33.4 to 66.6 % – in 16 % and with 66.7 to 100 % – in 8 % of patients. The existence of a prolonged QTc interval in each patient indicates that in its analysis it is necessary to base on the data of the AM of the ECG taking into account, except for the elongation and lengthening for a day.

KEY WORDS: hypertension, prolonged QTc interval, outpatient monitoring of ECG, types of daily blood pressure profile

ПИТОМА ВАГА ПАЦІЄНТІВ ІЗ АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ В ГРУПАХ ТЕРМІНУ ПОДОВЖЕНОГО ЗА ДОБУ ІНТЕРВАЛУ QTc ЗА ДАНИМИ АМБУЛАТОРНОГО МОНІТОРУВАННЯ ЕКГ В ЗАЛЕЖНОСТІ ВІД КЛІНІЧНИХ ОЗНАК

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Проведено вивчення питомої ваги у 82 пацієнтів з АГ в групах різного терміну подовженого за добу інтервалу QTc за даними АМ ЕКГ в залежності від клінічних ознак. В залежності від терміну подовженого QTc за добу пацієнтів відносили до однієї з трьох груп: група 1 – термін подовженого за добу інтервалу QTc від 0 до 33,3 %, група 2 – від 33,4 до 66,6 %, група 3 – від 66,6 до 100 %. Визначалася питома вага пацієнтів з АГ в групах терміну подовженого інтервалу QTc в залежності від віку, статі, ваги пацієнтів, типу циркадного індексу ЧСС, стадії, ступеню та давності ГХ, наявності ішемічної хвороби серця, ФК і стадії ХСН та цукрового діабету. За даними АМ ЕКГ подовжений інтервал QTc має місце у кожного пацієнта з АГ, при цьому з рівнем підвищення від 0 до 33,3 % від доби він виявлється у 76 %, з 33,4 до 66,6 % – у 16% і з 66,7 до 100 % – у 8 % пацієнтів. Існування подовженого інтервалу QTc у кожного пацієнта свідчить, що в його аналізі необхідно грунтуватися на даних АМ ЕКГ з урахуванням, окрім самого подовження, його терміну за добу.

КЛЮЧОВІ СЛОВА: артеріальна гіпертензія, подовжений інтервалу QTc, амбулаторне моніторування ЕКГ, типи добового профілю артеріального тиск

УДЕЛЬНЫЙ ВЕС ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В ГРУППАХ УДЛИНЕННОГО ЗА СУТКИ ИНТЕРВАЛА QTc ПО ДАННЫМ АМБУЛАТОРНОГО МОНИТОРИРОВАНИЯ ЭКГ В ЗАВИСИМОСТИ ОТ КЛИНИЧЕСКИХ ПРИЗНАКОВ

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Проведено изучение удельного веса у 82 пациентов с АГ в группах разного срока удлиненного за сутки интервала QTc по данным АМ ЭКГ в зависимости от клинических признаков. В зависимости от

срока удлиненного QTc за сутки пациентов относили к одной из трех групп: группа 1 – срок удлиненного за сутки интервала QTc от 0 до 33,3 %, группа 2 – от 33,4 до 66,6 %, группа 3 – от 66,6 до 100 %. Определялся удельный вес пациентов с АГ в группах удлиненного интервала QTc в зависимости от возраста, пола, веса пациентов, типа циркадного индекса ЧСС, стадии, степени и давности АГ, наличии ишемической болезни сердца, ФК и стадии ХСН и сахарного диабета. По данным АМ ЭКГ удлиненный интервал QTc имеет место у каждого пациента с АГ, при этом с уровнем повышения от 0 до 33,3 % за суток он выявляется в 76 %, с 33,4 до 66,6 % – в 16 % и с 66,7 до 100 % – у 8 % пациентов. Существование удлиненного интервала QTc у каждого пациента свидетельствует о том, что в его анализе необходимо основываться на данных АМ ЭКГ с учетом, кроме самого удлинения и на его срок удлинения за сутки.

КЛЮЧЕВЫЕ СЛОВА: артериальная гипертензия, удлиненный интервал QTc, амбулаторное мониторирование ЭКГ, типы суточного профиля артериального давления

INTRODUCTION

Hypertension significantly increases the risk of cardiovascular complications and premature death [1–2]. Attention is drawn to the estimation of daily fluctuations of the interval QTc, since even with its short-term growth, the duration of the «vulnerable» period of the cardiac cycle and the propensity to develop paroxysms «pirouette-tachycardia» [3] may increase. A study on AM EKG of the electrophysiological phenomenon of the prolonged interval QTc, as an independent predictor of fatal rhythm disturbances leading to premature death [4–7], allowed not only to determine the minimum, average and maximum QTc interval, but also to establish the length of the interval QTc per day [8].

At the same time, no studies have yet been conducted to study the effects of different levels of prolonged QTc in AM of ECG in patients with hypertension due to its clinical features.

OBJECTIVE

The aim of the work is to study the proportion of patients with hypertension in groups of varying duration of QTc prolonged per day according to the AM of the ECG, depending on the clinical signs.

The study was conducted as a part of research work «Pharmacological and intervenetional approaches to the treatment of patients with heart rate disorders and arterial hypertension», state registration 0116U000973.

MATERIALS AND METHODS

82 patients were examined in the outpatient clinic No. 24 in Kharkiv (28 male and 54 female, age 33–76 years old, with duration of EH from first identified till 30 yers lasting.

The main group of patients with hypertension consisted of patients with stage II – 72 %, with stage I – 15 %, with the third – 13 %. The mild degree of hypertension occurred in 51 % of patients, moderate – 29 %, severe – at 20 %. Of the total number of registered patients with hypertension, the proportion of coronary heart disease (CHD) was 73 %, of which: diffuse cardiosclerosis (DC) – 52 %, stable angina pectoris – 18 %, focal cardiosclerosis – 2 %. Patients with EH without coronary artery disease – 27 %. The second functional class of CHF (FC CHF) is registered in 40 %, I – in 28 %, III – in 5 %. Chronic heart failure (CHF) stage I is registered in 43 %, and IIIA – at 30 %.

The study did not include people with acute cardiovascular disease, with stable angina pectoris IV FC, CHF IIB – III stages and IV FC CHF, thyroid diseases, with chronic diseases in the stage of exacerbation.

The QT interval (QTc) was corrected using the Bazzet formula [9–10] with the use of the combined Holter ECG monitor ECG and BP - «Cardio Sens AT». Calculation of indicators was carried out with the help of the program «Cardio Sens».

Depending on the duration of prolonged QTc per day, the patients were assigned to one of three groups: group 1 – the term extended by day of the interval QTc from 0 to 33.3 %, group 2 – from 33.4 to 66.6 %, group 3 – from 66.6 to 100 %.

The proportion of patients with hypertension in the groups of the prolonged QTc interval depending on age, sex, weight of patients, type of circadian heart rate index, stage, degree and prescription of hypertension, presence of ischemic heart disease, FC and stage of CHF and diabetes mellitus were determined.

To determine the frequency of occurrence of clinical signs of hypertension, depending on the proportion of prolonged QTc, the frequency relation (P) and its error (p %) were estimated.

The calculations were performed on a personal computer using program «Microsoft Office Excel 2010».

RESULTS AND DISCUSSION

The results of the study of the proportion of patients with hypertension in the groups of the prolonged QTc interval per day at the AM of the ECG as a whole and depending on age, sex, body mass index and circadian heart rate index are presented in Table 1. According to all the clinical signs, the group 1 was the largest, which accounted for 76 % of all patients. With an increase in the number of patients, the proportion of patients progressively decreased, making up for the group 2 – 16 % and for the group 3–8 %.

Table 1

The proportion of patients with hypertension in QTc-prolonged group (P (%), p %) for the outpatient monitoring of the ECG as a whole and depending on age and sex, body mass index and circadian heart rate index

Clinical manifestation	Graduation of clinical features	The proportion of patients in QTc-prolonged groups (P (%), p %)					
		Group 1 0–33,3, N = 62		Group 2 33,4–66,6, N = 13		Group 3 66,7–100, N = 7	
		P	p %	P	p %	P	p %
Age, years	Adulthood	45	5,5	31	13,3	43	20,2
	Old age	55	5,5	69	13,3	57	20,2
Gender	Female	60	5,5	77	12,2	100	0,0
	Male	40	5,5	23	12,2	0	0,0
BMI, kg/m^2	Normalweight	13	3,7	0	0,0	14	14,3
	Overweight	34	5,3	38	14,0	14	14,3
	Obesity I	29	5,0	46	14,4	43	20,2
	Obesity II	18	4,2	15	10,4	14	14,3
	Obesity III	6	2,7	0	0,0	14	14,3
Circadian index	Normal	56	5,5	8	7,7	57	20,2
	Low	39	5,4	85	10,4	43	20,2
	High	5	2,4	8	7,7	0	0,0

Note: N – number of surveys; P – specific gravity; QTc – corrected QT.

In the study of age-related features, group 1 is the largest. The proportion of elderly patients is highest in all three groups.

Group 1 was the highest among both male and female patients, but an increase in the proportion of patients with prolonged QTc occurred only among female patients. The work in which the proportion of prolonged QTc was studied based on the data of outpatient ECG monitoring, we were not found in domestic or foreign literature, but our results are mediated but confirm the facts of prolongation of the interval QTc among the female [4].

In the BMI analysis, group 1 was also the largest. The proportion of patients with overweight and obesity grade I was significantly superior to group 1 and group 2. As the number of the group increased, the proportion of patients with obesity I and III degrees corresponded to the literature [11–13].

In the study of the circadian heart rate index, group 1 was the largest. On the background of an increase in the serial number of the group there was a progressive increase in the proportion of patients with normal and reduced circadian heart rate index.

The proportion of patients with hypertension in prolonged QTc groups depending on the stage and degree of EH and the age of the disease are presented in Table 2.

In analyzing the stages and degrees of EH, group 1 was the largest. On the background of a decrease in the proportion of patients with stage I and mild to moderate degree of EH in groups

2 and 3, there was a progressive increase in the proportion of patients with stage II and severe EH in the same groups.

With the increase in the number of the group in the background of a gradual decrease in the proportion of patients with a history of the disease from 1 to 5 years and the unchanged level of patients with a disease aged 6 to 10 years, there was a progressive increase in the proportion of the disease more than 10 years.

The proportion of patients with hypertension with AM ECG depending on the CHD, the stages of CHF and FC CHF, the presence of diabetes mellitus are presented in Table 3.

Table 2

The proportion of patients with hypertension in QTc-prolonged group (P (%), p %) for the outpatient monitoring of the ECG depending on the stage and degree o f hypertension, the prescription of the disease

Clinical manifestation	Graduation of clinical features	The proportion of patients in QTc-prolonged groups (P (%), p %)					
		Group 1 0–33,3, N = 62		Group 2 33,4–66,6, N = 13		Group 3 66,7–100, N = 7	
		P	p %	P	p %	P	p %
Stages of EH	I	18	4,2	8	7,7	0	0,0
	II	68	5,2	85	10,4	86	14,3
	III	15	3,9	8	7,7	14	14,3
Degrees of EH	Mild	55	5,5	46	14,4	29	18,4
	Moderate	27	5,0	46	14,4	14	14,3
	Severe	18	4,2	8	7,7	57	20,2
Duration, years	For the first time	9	3,3	8	7,7	0	0,0
	1–5	37	5,4	46	14,4	29	18,4
	6–10	29	5,0	23	12,2	29	18,4
	> 10	24	4,8	23	12,2	43	20,2

Note: N - number of surveys; P- specific gravity; QTc – corrected QT.

Table 3

The proportion of patients with hypertension in QTc-prolonged group (P (%), p %) f or the outpatient monitoring of the ECG depending on CHD, CHF and FC CHF, and the presence of diabetes mellitus

Clinical manifestation		Graduation of clinical features	The proportion of patients in QTc-prolonged groups (P (%), p %)					
			Group 1 0–33,3, n = 62		Group 2 33,4–66,6, n = 13		Group 3 66,7–100, n = 7	
			P	p %	P	p %	P	p %
IHD		In total	71	5,0	77	12,2	86	14,3
		Stable angina	19	4,4	15	10,4	14	14,3
		Diffuse cardiosclerosis	48	5,6	62	14,0	71	18,4
		Focal cardiosclerosis	3	2,0	0	0,0	0	0,0
		Absence of IHD	29	5,0	23	12,2	14	14,3
CHF		Total	71	5,0	77	12,2	86	14,3
CHF	FC	I	24	4,8	38	14,0	43	20,2
		II	42	5,5	38	14,0	29	18,4
		III	5	2,4	0	0,0	14	14,3
	Stage	I	39	5,4	54	14,4	57	20,2
		II A	32	5,2	23	12,2	29	18,4
		Without CHF	29	5,0	23	12,2	14	14,3
Diabetes mellitus		DM 2 type	13	3,7	15	10,4	14	14,3
		Absence of DM	87	3,7	85	10,4	86	14,3

Note: N – number of surveys; P – specific gravity; QTc – corrected QT.

In the analysis of the proportion of patients in groups of prolonged QTc, a decrease in the number of patients without coronary artery disease and an increase in CHD were observed in the group with an increase in the number of the group due to an increase in patients with DC in groups 2 and 3. In the study of the proportion of patients without CHF and its presence in the groups 2 and 3, there was a decrease in the proportion of patients without CHF and an increase in the proportion of CHF, due to FC I, III and, most of all, CHF stage I. This is most likely due to the small number of patients in group 3 [14–15].

The increase in the number of the group indicated an increase in the proportion of patients with diabetes and a decrease in the proportion of patients without diabetes.

The results are new. The fact that every patient with hypertension recorded long QTc interval requires in clinical practice, taking into account its effects on possible risks of emergency, it is mandatory to conduct AM of the ECG. In this case, it is important to take into account not only the elongation of the interval, but also the specific weight of its lengthening for a day.

The data obtained explain the increase in the risk of life-threatening arrhythmias in patients with hypertension and prolonged QTc intervals, even in cases where long-term QTc were not detected based on the results of a standard ECG [11].

CONCLUSIONS

1. According to the AM ECG, the prolonged QTc interval occurred in each patient with hypertension, with an increase from 0 to 33.3 % of the day it was 76 %, from 33.4 to 66.6 % - 16 % and from 66.7 % to 100 % – in 8 % of patients.

2. The term of the prolonged interval QTc from 0 to 33.3 % of the day was most commonly found in elderly, female, overweight, normal circadian index of heart rate, stage II and mild degree of hypertension, with the duration of EH from 1 to 5 years, in the presence of CHD and CHF and in patients without diabetes.

3. The term of the prolonged interval QTc from 33.4 to 66.6 % of the day was most commonly found in elderly, female, obese, I-grade, lowered circadian heart rate index, stage II, and mild to moderate hypertension, with a long history of the disease 1 to 5 years, in the presence of coronary heart disease, due to DC and CHF and in patients without diabetes.

4. The term of the prolonged interval QTc from 66.7 to 100 % of the day was most commonly found in elderly, female, obese, and normal, and lowered circadian heart rate index, stage II and severe EH, with a disease history of more than 10 years, in the presence of coronary heart disease, due to DC and CHF and in patients without diabetes.

5. The existence of the prolonged QTc interval in each patient indicates that in its analysis it is necessary to base itself on the data of the AM of the ECG taking into account, apart from the extension itself, its term for a day.

PROSPECTS FOR FUTURE STUDIES

The prospect of further research is the study of the effect of medical treatment of antihypertensive drugs for the prolonged QTc interval.

REFERENCES

1. Rekomendatsii Yevropeiskoi Asotsiatsii hipertenzii ta Yevropeiskoi Asotsiatsii kardiolohiv (ESH / ESC) po likuvanniu AH, 2013.
2. Rekomendatsii Ukrainskoi Asotsiatsii kardiolohiv z profilaktyky ta likuvannia arterialnoi hipertenzii. Posibnyk do Natsionalnoi prohramy profilaktyky i likuvannia arterialnoi hipertenzii. – K.: PP VMB; 2008. – 80 s.
3. Diagnostyka ta likuvannia extrasystolii ta parasystolii // Rekomendatsii Robochoii grupy z poryshen rytmu sertsa Asotsiatsiia kardiolohiv Ukrainy: Kyiv, 2012 r. – S.20–21.
4. Rekomendatsii Asotsiatsii kardiolohiv Ukrainy. Likuvannia shlunochkovykh porushen sertsia ta profilaktyka raptovoi sertsevoi smerti: Kyiv, 2009 r. – S.43–45.
5. Yabluchanskyi N.Y., Martynenko A.V., Martymianova L.A. Ambulatornaia elektrokardyohrafyia / Seryia: dlia nastoiashchykh vrachei. – Kh.: – KhNU imeni. V. N. Karazyna, 2015, S. 113.
6. Breidthardt T., Christ M., Matti M. et al. QRS and QTc interval prolongation in the prediction of longterm mortality of patients with acute destabilised heart failure // Ibid. – 2007. – Vol. 93. – P. 1093–1097.

7. Grigioni F., Piovaccari G., Boriani G. Prolonged QRS and QTc interval and mortality // Heart. – 2007. – Vol 93(9). – P. 1093–1097.
8. Rozpodil tryvalosti intervalu QTc za danymy ambulatornoho monitoryvannia EKG u khvorykh z hypertonichnoiu khvoroboiu v zalezhnosti vid klinichnykh proiaviv. / Tselik N. E., Shmidt O. Y., Martinenko O. V., Yabluchansky M. I. // Kafedra vnutrishnoi meditsyna Kharkivskogo natsionalnoho universytetu imeni V. N. Karazina, Ukraina // Visnyk Kharkivskogo natsionalnoho universytetu imeni V. N. Karazina, Seriia «Medicina». – 2017. – No. 33.
9. Hiroshi M. The QT syndromes: long and short / M. Hiroshi, W. Jiashin, P. Douglas // Lancet. – 2008. – No. 372. – C. 750–763.
10. Moss A. Long QT syndrome / A. Moss J. Robinson // Heart Dis Stroke. – 1992. - No. 1. – C.309–314.
11. Kovalenko V. M. Kerivnytstvo po kardiologii. Chastyna 3, 2008 / V. M. Kovalenko, E. P. Svischenko, U. M. Sirenko. – K.: MORION, 2010. – S. 262–269.
12. Relationship of electrocardiographic repolarization measures to echocardiographic left ventricular mass in men with hypertension / K. Porthan, J. Virolainen, T. Hiltunen, M. Viitasalo, H. Vaananen, J. Dabek, T. Hannila-Handelberg, L. Toivonen, M. Nieminen, K. Kontula, L. Oikarinen [et al.] // J. Hypertens. – 2007. – C. 1951–1957.
13. Klinichni proiavy arterialnoii hipertenzii za riznyh diapazoniv tryvalosti intervalu QTc EKG. / Tselik N. E., Shevchuk M. I., Martynenko O. V. // Kafedra vnutrishnioii medytsiny Kharkivskoho natsionalnoho universitetu imeni V. N. Karazina, Ukraiina // Visnyk Kharkivskoho natsionalnoho universitetu imeni V.N. Karazina, Seriia «Medytsina». – 2015. – No. 30. – S. 41–44.
14. Pellerin D. Separation of autonomic tone and heart rate influences on ventricular repolarization variations using selected 24-hour electrocardiographic data in patients with heart failure / D. Pellerin, P. Maison-Blanche, J. S. Hermida, [et al.] // Ibid. – P. 282.
15. Kulyk V. L., Yabluchansky M. I. Interval QT v kardiolohichnii klinitsi. / «Visnyk Kharkivskoho natsionalnoho universitetu» – Kh.: – KhNU imeni V. N. Karazina, 2009. – No. 879. – S. 73–96.

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FUNCTIONAL CLASSES AND CLINICAL CHARACTERISTICS OF CHRONIC HEART FAILURE IN PATIENTS WITH ATRIAL FIBRILLATION AND/OR FLUTTER AFTER RADIOFREQUENCY ABLATION

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The combination of atrial fibrillation and/or flutter and chronic heart failure is a frequent problem for many patients. Radiofrequency ablation is effective in the strategy for controlling the rhythm of patients with atrial fibrillation and/or flutter, but always requires concomitant therapeutic support. The study involved 70 patients with atrial fibrillation and/or flutter after radiofrequency ablation which were divided into groups according to the functional class of chronic heart failure. Gender and age of patients; types of ischemic heart disease; stages of chronic heart failure; degrees of arterial hypertension; the form of atrial fibrillation and flutter; class EHRA; the presence of diabetes mellitus type 1 or 2 we evaluated. The female sex prevailed in the group of II functional class of chronic heart failure than in I functional class or III functional class. Ischemic heart disease, first of all angina of effort, in patients with III functional class of chronic heart failure was significantly more frequent. In group of III functional class of chronic heart failure there were significantly more patients with 3 degrees of arterial hypertension. Male patients, regardless of functional class of chronic heart failure, more often than females are conducted invasive methods of treatment for atrial fibrillation/flutter. With increasing of functional class of angina the functional class of chronic heart failure is increasing. Among patients II and III functional class of chronic heart failure prevails the arterial hypertension III degree, which may be a predictor of adverse prognosis.

KEY WORDS: clinical characteristics, atrial fibrillation; atrial flutter, chronic heart failure, catheter ablation

ФУНКЦІОНАЛЬНІ КЛАСИ ТА КЛІНІЧНІ ХАРАКТЕРИСТИКИ ХРОНІЧНОЇ СЕРЦЕВОЇ НЕДОСТАТНОСТІ У ХВОРИХ НА ФІБРИЛЯЦІЮ ТА/АБО ТРІПОТІННЯ ПЕРЕДСЕРДЬ ПІСЛЯ РАДІОЧАСТОТНОЇ АБЛЯЦІЇ

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Поєднання фібриляції (тріпотіння) передсердь та хронічної серцевої недостатності є частою проблемою для багатьох пацієнтів. Радіочастотна абляція ефективна у стратегії контролю ритму пацієнтів з фібриляцією та/або тріпотінням передсердь, але завжди вимагає супутньої терапевтичної підтримки. У дослідженні взяли участь 70 пацієнтів з фібриляцією та/або тріпотінням передсердь після радіочастотної абляції, які були розділені на групи відповідно до функціонального класу хронічної серцевої недостатності. Стать і вік пацієнтів; типи ішемічної хвороби серця; ступені артеріальної гіпертензії; форми фібриляції (тріпотіння) передсердь; клас EHRA; наявність цукрового діабету 1 або 2 типу – були оцінені. Жіноча стать переважала у групі II функціонального класу хронічної серцевої недостатності, ніж у I функціональному класі або III функціональному класі. Ішемічна хвороба серця, а, насамперед, стабільна стенокардія, у пацієнтів з хронічною серцевою недостатністю III функціонального класу була значно частішою. У групі III функціонального класу хронічної серцевої недостатності виявилося значно більше пацієнтів з 3 ступеню артеріальної гіпертензії. Пацієнтам чоловічої статі, незалежно від функціонального класу хронічної серцевої недостатності частіше, ніж жінкам, проводять інвазивні методи лікування фібриляції/ тріпотіння передсердь. При збільшенні функціонально класу стенокардії функціональний клас хронічної серцевої недостатності зростає. Серед пацієнтів II та III функціонального класу хронічної серцевої недостатності переважає артеріальна гіпертензія 2 ступеню, що може бути предиктором несприятливого прогнозу.

КЛЮЧОВІ СЛОВА: клінічна характеристика, фібриляція передсердь, трепотіння передсердь, хронічна серцева недостатність, катетерна абляція

ФУНКЦИОНАЛЬНЫЕ КЛАССЫ И КЛИНИЧЕСКИЕ ХАРАКТЕРИСТИКИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ФИБРИЛЛЯЦИЕЙ И/ИЛИ ТРЕПЕТАНИЕМ ПРЕДСЕРДИЙ ПОСЛЕ РАДИОЧАСТОТНОЙ АБЛЯЦИИ

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Сочетание фибрилляции (трепетания) предсердий и хронической сердечной недостаточности является частой проблемой для многих пациентов. Радиочастотная абляция эффективна в стратегии контроля ритма пациентов с фибрилляцией и/или трепетанием предсердий, но всегда требует сопутствующей терапевтической поддержки. В исследовании приняли участие 70 пациентов с фибрилляцией и/или трепетанием предсердий после радиочастотной абляции, которые были разделены на группы в зависимости от функционального класса хронической сердечной недостаточности. Пол и возраст пациентов; типы ишемической болезни сердца; степени артериальной гипертензии; формы фибрилляции (трепетания) предсердий; класс EHRA; наличие сахарного диабета 1 или 2 типа – были оценены. Женский пол преобладала в группе II функционального класса хронической сердечной недостаточности, чем в I функциональном классе или III функциональном классе. Ишемическая болезнь сердца, а, прежде всего, стабильная стенокардия, у пациентов с хронической сердечной недостаточностью III функционального класса была значительно более частой. В группе III функционального класса хронической сердечной недостаточности оказалось значительно больше пациентов с 3 степени артериальной гипертензии. Пациентам мужского пола, независимо от функционального класса хронической сердечной недостаточности, чаще, чем женщинам, проводят инвазивные методы лечения фибрилляции /трепетания предсердий. При увеличении функционально класса стенокардии функциональный класс хронической сердечной недостаточности возрастает. Среди пациентов II и III функционального класса хронической сердечной недостаточности преобладает артериальная гипертензия 2 степени, что может быть предиктором неблагоприятного прогноза.

КЛЮЧЕВЫЕ СЛОВА: клиническая характеристика, фибрилляция предсердий, трепетание предсердий, хроническая сердечная недостаточность, катетерная абляция

INTRODUCTION

The combination of atrial fibrillation and/or flutter and chronic heart failure is a frequent problem for many patients [1].

These diseases have similar risk factors and common pathophysiology. Chronic heart failure and atrial fibrillation and/or flutter exacerbate each other through mechanisms of cardiac remodeling, activation of neurohumoral mechanisms and insufficient left ventricular function [2–3].

Many studies have shown that the presence of atrial fibrillation and/or flutter is associated with an unfavorable prognosis for chronic heart failure, regardless of the systolic function of the left ventricle [1, 3–4].

During the past three decades, catheter and surgical ablation of AF have evolved from investigational procedures to their current role as effective treatment options for patients with atrial fibrillation. Catheter ablation of atrial fibrillation is even more widely available, and is now the most commonly performed catheter ablation procedure [5–6].

Radiofrequency ablation is effective in the strategy for controlling the rhythm of patients with atrial fibrillation and/or flutter [6–7], but always requires concomitant therapeutic support. The presence of chronic heart failure in these individuals greatly influences the management, especially depending on the functional class of chronic heart failure, but this issue has not been studied too much.

OBJECTIVE

To evaluate clinical characteristics of chronic heart failure in patients with atrial fibrillation and/or flutter after radiofrequency ablation depending on functional class of chronic heart failure.

MATERIALS AND METHODS

On the basis SI «Zaycev V. T. Institute of General and Urgent Surgery NAMS of Ukraine», Kharkiv, Ukraine 70 patients with atrial fibrillation and/or flutter at age 61 ± 8 (p (M ± sd)) (44 men and 26 women) in the department of ultrasound and clinical-instrumental diagnosis and minimally invasive interventions were examined. Patients after radiofrequency ablation (RFA) of arrhythmia were divided into groups according to the functional class (FC) of chronic heart failure

(CHF) according to New York Heart Association (NYHA) Functional Classification: 22 patients with CHF I FC, 29 – II FC, 19 – III FC. Patients IV FC CHF were absent.

We evaluated gender and age of patients; types of ischemic heart disease (IHD) (angina of effort and functional classes (FC) according Canadian Cardiovascular Society, past myocardial infarction (PMI)) [8–9]; CHF stages (I–III) according to the classification of Strazhesko M. D. and Vasilenko V. H., degrees of arterial hypertension (AH) (1–3) [9], the form of AF and AFL (paroxysmal, persistent, long-standing persistent, permanent); class EHRA (I–IV) according to the classification of the European Association for Heart Rate [6]; the presence of diabetes mellitus (DM) type 1 or 2.

The above indicators were evaluated for 5–7 days after surgery. The data obtained after the formation of the database processed in Microsoft Excel, Statistica 10. For statistical evaluation of the results were used parametric criterias (mean – M, standard deviation – sd), non-parametric criterias (absolute (n, number), relative (percentage (%) and the average error rate (sP)). The binary data of the independent samples were expressed in parts, the statistical significance of the differences was determined using t – criteria, the level of significance was set at 0,05. The reliability of the differences was also confirmed by the method of confidence intervals. The results were considered reliable at levels of significance $p < 0,05$.

The research was carried out within the Scientific research work; ID 0116U000973 from 12.2016.

RESULTS AND DISCUSSION

Table presents the data of characteristics of chronic heart failure in patients with AF/AFL after ablation depending on the FC CHF.

It was found that most patients were male, but no quantitative differences were found depending on FC CHF.

The female sex prevailed in the group of II FC CHF than I FC or III FC.

IHD in patients with III FC CHF was significantly more frequent than among patients with I FC or II FC.

Angina of effort was significantly more frequent among the group of patients III FC CHF.

Among group of I FC CHF was predominated angina of effort II FC, among group II FC CHF in more than a percentage of cases registered angina of effort III FC; among group III FC CHF – angina of effort III FC and PMI.

Depending on the stage of CHF, in all three groups, patients with II A stage CHF predominated.

Among the whole group of patients with AH, 3 degrees were observed more often than 1 degree. Most significantly AH was registered among the group II FC CHF and III FC CHF than among those belonging to group I FC.

In group III of FC CHF there were significantly more patients with 3 degrees of AH, in group I and II of FC CHF there were no significant differences depending on the degree of hypertension.

In the whole group of patients, AF was dominant, and the persistent form was the most common.

The frequency of detection of AF, depending on FC CHF, had no significant differences.

Within the groups of FC CHF differences in the form (paroxysmal, persistent, long-standing persistent, permanent), there are no significant differences, except for the group II FC, where greater proportion had persistent form.

Among surveyed significant differences in the frequency of AFL detection in different groups of FC CHF were not found.

Persistent form of AFL prevailed over others; it was at the same frequency in all groups of FC CHF.

By classes EHRA in all FC CHF is significantly prevailing III class; IV class EHRA is more common in group III FC CHF.

In all groups patients with type 1 diabetes were absent. Type 2 diabetes occurred only in patients with III FC CHF.

Based on our results, interventions due to AF/AFL are performed more often in male patients, but this is independent from FC CHF. In a study by Schnabel R.B. and others [6] were showed that women were more symptomatic but less likely to receive invasive methods for restoring the rhythm, such as electrical cardioversion or ablation. Further research is needed to confirm that these differences do not impede women with AF/AFL.

II FC CHF was prevailed among women who had ablation. This feature is not found in the literature, therefore, requires further research.

Table

Clinical characteristics of chronic heart failure in patients with AF/AFL after ablation depending on the FC CHF

Clinical data			Total	FC CHF		
				I FC	II FC	III FC
Number (n, % ± sP)			70	22 (31,5 ± 6)	29 (41,4 ± 5)	19 (27,1 ± 5)
Age, years (M ± sd)			61 ± 8	56 ± 8	62 ± 8	65 ± 8
Gender (n (% ± sP))	Males		44 (62,8 ± 5,8) •	14 (31,8 ± 7,1)	16 (36,4 ± 7,3)	14 (31,8 ± 7,1)
	Females		26 (37 ± 6) •	8 (30,7 ± 7,2)	13 (50 ± 10) **	5 (19,2 ± 7,5) **
IHD (n (% ± sP))	Total		26 (100)	4 (15,4 ± 7,2)	5 (19,2 ± 7,9)	17 (65,4 ± 9,5) *
	Angina of effort		22	4 (18,2 ± 8,4)	6 (27,3 ± 9,7)	12 (54,5 ± 10,9) **
	FC of angina	I	1 (5 ± 3)	1 (25 ± 5)	-	-
		II	9 (43 ± 6)	3 (75 ± 5)	2 (33 ± 6)	4 (33 ± 6)
		III	11 (52 ± 6)	-	4, 67 ± 6	8, 67 ± 6
		IV	-	-	-	-
	PMI		5 (19 ± 5)	-	-	5 (29 ± 5)
CHF stages ((n (% ± sP))	I		29 (41 ± 6)	22 (100)	7 (24 ± 5)	-
	II A		34 (49 ± 6)	-	22 (76 ± 5)	12 (63 ± 6) $^{\Delta}$
	II B		7 (10 ± 4)	-	-	7 (37 ± 6)
	III		-	-	-	-
AH (n (%±sP))	Total		41 (59 ± 6)	9 (21,9 ± 6,5)**	18 (43,9 ± 7,8) **	14 (34,1 ± 7)
	Degree	I	2 (5 ± 3)	-	2 (11 ± 4)	0
		II	16 (39 ± 6) •	6 (67 ± 6)	7 (39 ± 6)	3 (21 ± 5) •
		III	23 (56 ± 6) •	3 (33 ± 6)	9 (50 ± 6)	11 (79 ± 5) •
AF (n (%±sP))	Total		51 (72,8 ± 5,3)	16 (31,4 ± 6,5)	21 (41,2 ± 6,9)	14 (27,4 ± 6,3) $^{\Delta}$
	Paroxysmal		15 (29,4 ± 6,4)	6 (38,0 ± 12,5)	5 (23,8 ± 9,5) ••	4 (28,6 ± 12,5)
	Persistent		31 (60,8 ± 6,9) ••	10 (63 ± 12,5)	15 (71,4 ± 10,1) ••	6 (42,9 ± 13,7)
	Long-standing persistent		-	-	-	-
	Permanent		5 (10 ± 4)	-	1 (5 ± 3)	4 (29 ± 5)
AFL (n (%±sP))	Total		44 (63 ± 6)	15 (34,1 ± 7,2)	18 (40,9 ± 7,5)	11 (25 ± 6,6)
	Paroxysmal		7 (16 ± 5,5) ••	3 (20 ± 10,7) ••	3 (16,7 ± 9) ••	1 (9 ± 9) ••
	Persistent		35 (80 ± 6,2) ••	11 (73,3 ± 11,8) ••	15 (83,3 ± 9) •• $^{\Delta}$	9 (81,9 ± 12,2) •• $^{\Delta}$
	Long-standing persistent		2 (5 ± 2)	1 (7 ± 3)	-	1 (9 ± 9)
	Permanent		-	-	-	-
EHRA (n (%±sP))	I		-	-	-	-
	II		4 (6 ± 3)*	3 (14 ± 4) •	1 (3 ± 2) •	-
	III		61 (87 ± 4) •	19 (86 ± 4) • $^{\Delta}$	27 (93 ± 3) • $^{\Delta}$	15 (79 ± 5) • $^{\Delta}$
	IV		5 (7 ± 3) *	-	1 (3 ± 2)	4 (21 ± 5) •
DM (n (%±sP))	Type	I	-	-	-	-
		II	4 (6 ± 3)	-	-	4 (21 ± 5)

*Note: M – mean; n – number; sd - standard deviation; sP - the average error rate; $^{\Delta}$ - p > 0,05 the difference between FCs; • p < 0,05 the difference inside the group, FC; •• p = 0,001 the difference inside the group, FC; ** p < 0,05 between FC; * p = 0,001 between FC.*

Angina of effort was prevalent in patients of III FC CHF. FC CHF and FC of agina had a direct dependence: with the growth of FC angina the FC CHF grew. This fact can be explained [7] that AF/AFL is associated with a higher severity of IHD, which can lead to CHF through the progression of IHD and changes in the left ventricle function. In his time Davies M. J. and Pomerance A. in their study on deceased patients with AF suggested that patients with IHD had a primary risk of developing AF/AFL than CHF, which was also reflected in the study by Motloch J. and others [8].

Our study showed that patients with II and III FC CHF more often had an AH III degree and, as shown in the Sahle B.W. study and others [9], these patients have an unfavorable prognosis, especially for males.

We found the predominance of the persistent AF/AFL form over the other in all groups of FC CHF associated with a poorer rhythm control in this form with medication therapy as were shown in the study of Mittal S. et al. [10].

It has been found that in patients with III FC CHF, according to EHRA, arrhythmia has a more severe course clinically, that has not yet been adequately studied.

CONCLUSIONS

1. Male patients regardless of the functional class of chronic heart failure more often than females invasive methods of treatment for atrial fibrillation and/or flutter are conducted.

2. Angina of effort is more commonly observed in patients of III functional class of chronic heart failure; functional class of chronic heart failure is increasing with increasing of the functional class of angina.

3. Among patients II and III of functional class of chronic heart failure prevails arterial hypertension III degree, which may be a predictor of adverse prognosis.

4. Regardless of the functional class of chronic heart failure, the persistent form of atrial fibrillation and/or flutter predominates over other forms, due to the poor control of the rhythm by drug therapy.

In the III functional class of chronic heart failure, according to EHRA, the clinical manifestation of arrhythmia is more severe.

PROSPECTS FOR FUTURE RESEARCHES

It seems to be appropriate to study further clinical course of AF and AFL after RFA at various stages depending on the FC of CHF and to find is there are specific characteristics of drug therapy.

REFERENCES

1. Kotecha D. Atrial fibrillation in heart failure: what should we do? / D. Kotecha, J. P. Piccini. // European Heart Journal. – 2015. – No. 36. – P. 3250–3257.
2. Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure [Electronic source] / [L. Gigli, P. Ameri, G. Secco et al.] // World journal of cardiology. – 2016. – Link: https://www.wjgnet.com/1949-8462/journal/v8/i11/index.htm.
3. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) [Electronic source] // European Heart Journal. – 2016. – Link: http://eurheartj.oxfordjournals.org/content/ehj/early/2016/09/08/eurheartj.ehw210.full.pdf
4. 2013 ESC Guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology (ESC) // Journal of Heart Failure. – 2013. – No. 34. – P. 2949–3003.
5. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) // Journal of Heart Failure. – 2016. – No. 37. – P. 2129–2200.
6. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation / [R. B. Schnabel, L. Pecen, F. M. Ojeda et al.]. // British Cardiac Society. – 2017. – No. 103. – P. 1024–1030.
7. Corradi D. Atrial fibrillation from the pathologist's perspective / Domenico Corradi. // Cardiovascular Pathology. – 2014. – No. 23. – P. 71–84.
8. Characteristics of coronary artery disease among patients with atrial fibrillation compared to patients with sinus rhythm [Electronic source] / [L. J. Motloch, S. Reda, R. Larbig et al.] // Hellenic Journal of Cardiology. – 2017. – Link: http://dx.doi.org/10.1016/j.hjc.2017.03.001.

9. Long-term survival following the development of heart failure in an elderly hypertensive population [Electronic source] / [B. W. Sahle, A. J. Owen, L. M. Wing et al.] // Cardiovascular Therapeutics. – 2017. – Link: http://onlinelibrary.wiley.com/doi/10.1111/1755-5922.12303/abstract;jsessionid=23E24499751AC29865AC14B77901DD71.f03t03.
10. Mittal S. Differentiating Paroxysmal From Persistent Atrial Fibrillation / Suneet Mittal. // Journal of the American College of Cardiology. – 2014. – No. 63. – P. 2849–2851.

Clinical case

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ANTISYNTHETASE SYNDROME: COURSE OF A RARE DISEASE ON EXAMPLE OF CLINICAL CASE

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Systemic disorders of connective tissue refer to rare and poorly studied diseases. This group of diseases associated with the variable course and makes it interesting for either medical scientists and researchers or practitioner. Herein we report a case of antisynthetase syndrome with interstitial lung disease complicated by pulmonary thromboembolism. The patient is 71 year old female, who suffered from severe dyspnea, dry cough, intermittent wheezing. Also she had dry eyes, dry mouth, muscle weakness and intermittent pain in large joints, and low grade fever. Physical examination revealed a characteristic heliotrope eye rash, V sign, «mechanic's hand», peripheral muscles atrophy, dry eyes and mouth, fine crackles to auscultation in basal parts of lungs, soft S1 and S2 heart sounds. Her biochemical profile showed increased creatinekinase, LDH, AsAT, and AlAT Her immunology results were positive to ANA, anti-ds-DNA, anti-ss-A, anti-ss-B and anti-Jo-1 autoantibodies. Based on the obtained data, antisynthetase syndrome was established. It was detected, that progressive dyspnea had been caused by interstitial lung disease and pulmonary thromboembolism. It was confirmed by chest CT-scan and pulmonary angiography. Treatment in this case is mainly symptomatic. It was prescribed glucocorticoids, immunosuppressant, and anticoagulants. This case illustrates the course of the antisynthetase overlap syndrome and difficulties of it management due to the lack of treatment standards and reliable data of the medicine effectiveness.

KEY WORDS: overlap syndrome, antisynthetase syndrome, anti-Jo-1 autoantibodies, interstitial lung disease, pulmonary thromboembolism

АНТІСІНТЕТАЗНИЙ СИНДРОМ: ПЕРЕБІГ РІДКІСНОГО ЗАХВОРЮВАННЯ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Системні захворювання сполучної тканини відносяться до рідкісних і маловивчених хвороб. Клінічний перебіг даної групи захворювань варіабельний, що і робить їх привабливим об'єктом вивчення як для вчених, так і для практичних лікарів. У даній статті ми опишемо клінічний випадок антісінтетазного синдрому з інтерстиціальним ураженням легень, ускладнений тромбоемболією легеневої артерії. Пацієнт – 71-річна жінка зі скаргами на виражену задишку, сухий кашель, періодичний затруднений видих, що супроводжується свистом. Також у неї були присутні сухість очей і ротової порожнини, м'язова слабкість, періодичні болі в великих суглобах, субфебрильна температура. При об'єктивному огляді звертали на себе увагу характерний періорбітальний геліотропний сип, симптом V – еритема обличчя і шиї, «рука механіка», атрофія периферійних м'язів, сухість очей і порожнини рота, вологі дрібно пухирчасті хрипи в базальних відділах обох легень, глухі тони серця. В біохімічному аналізі крові відзначалося значне підвищення креатинфосфокінази, ЛДГ, АСТ, АЛТ. В імунологічному профілі були позитивні аутоантитіла до ANA, anti-ds-DNA, anti-ss-A, anti-ss-B і anti-Jo-1. На підставі отриманих даних, пацієнтці встановили діагноз антісінтетазний синдром. За допомогою комп`ютерної томографії грудної клітини та ангіографії легень було визначено, що прогресуюча задишка обумовлена інтерстиціальним ураженням легень та тромбоемболією легеневої артерії. Лікування в даному випадку симптоматичне. Пацієнтка отримувала глюкокортикостероїди, іммуносупресанти та антикоагулянтну терапії. Даний клінічний випадок

відображає перебіг антісінтетазного синдрому та труднощі в проведенні терапії через відсутність стандартів лікування й достовірних даних про ефективність препаратів.

КЛЮЧОВІ СЛОВА: оверлап синдром, антісинтетазний синдром, анті-Jo-1 аутоантітіла, інтерстіціальна хвороба легень, тромбоемболія легеневої артерії

АНТИСИНТЕТАЗНЫЙ СИНДРОМ: ТЕЧЕНИЕ РЕДКОГО ЗАБОЛЕВАНИЯ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Системные заболевания соединительной ткани относятся к редким и малоизученным болезням. Клиническое течение данной группы заболеваний вариабельно, что и делает их привлекательным объектом изучения, как для ученых, так и для практических врачей. В данной статье мы изложим клинический случай антисинтетазного синдрома с интерстициальным поражением легких, осложненный тромбоэмболией легочной артерии. Пациент – 71-летняя женщина с жалобами на выраженную одышку, сухой кашель, периодический затрудненный выдох сопровождающийся свистом. А также у нее присутствовали сухость глаз и полости рта, мышечная слабость, периодические боли в крупных суставах, субфебрильная температура. При объективном осмотре обращали на себя внимания характерная периорбитальная гелиотропная сыпь, симптом V – эритема лица и шеи, «рука механика», атрофия периферических мышц, сухость глаз и полости рта, мелкопузырчатые влажные хрипы в базальных отделах обеих легких, глухие тона сердца. В биохимическом анализе крови отмечалось значительное повышение креатинфосфокиназы, ЛДГ, АСТ, АЛТ. В иммунологическом профиле были положительные аутоантитела к ANA, anti-ds-DNA, anti-ss-A, anti-ss-B и anti-Jo-1. На основании полученных данных, пациентке был установлен диагноз антисинтетазный синдром. С помощью компьютерной томографии грудной клетки и ангиографии легких было определено, что прогрессирующая одышка обусловлена интерстициальным поражением легких и тромбоэмболией легочной артерии. Лечение в данном случае симптоматическое. Пациентка получала глюкокортикостероиды, иммуносупрессанты и антикоагулянтную терапии. Данный клинический случай иллюстрирует течение антисинтетазного синдрома и трудности в проведении терапии из-за отсутствия стандартов лечения и достоверных данных об эффективности препаратов.

КЛЮЧЕВЫЕ СЛОВА: оверлап синдром, антисинтетазный синдром, анти-Jo-1 аутоантитела, интерстициальная болезнь легких, тромбоэмболия легочной артерии

INTRODUCTION

As many as 25 % of connective tissue disease patients present with features of systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, rheumatoid arthritis and Sjögren syndrome evolving concurrently or consecutively during the course of the disease. Frequently these circumstances make the diagnosis of a specific rheumatic disease difficult. It is still contentious whether or not overlap syndromes represent the coexistence of separate diseases, the broad clinical expression of the one rheumatic disease, or distinct clinical entities with distinctive etiology and pathogenesis [1]. «Overlap syndromes» refers to a diverse group of conditions that have clinical features of, and meet classification criteria for, more than 1 well-characterized rheumatic disease. Usually present subacutely with clinical manifestations that can include different organ systems. The pattern of organ involvement reflects the characteristic features of the well-defined rheumatic diseases occurring together. Overlap syndromes are characterized by specific clinical features, autoantibody profiles, and immunogenetics. Currently it distinguished following clinical forms of overlap syndromes:

- Mixed connective tissue disease (MCTD) is a distinct clinical entity characterized by overlapping features of SLE, scleroderma, myositis, and rheumatoid arthritis in the setting of a high titer of autoantibodies to a defined nuclear antigen, known as U1-ribonucleoprotein (U1-RNP, also called RNP or nRNP). Clinical features of MCTD are highly variable, involving prominently arthritis,

Raynaud phenomenon, sclerodermatous skin changes, and myositis. Severe central nervous system and renal diseases are rare manifestations.

- Antisynthetase syndromes form a distinct group characterized by the presence of antibodies directed against various aminoacyl-tRNA synthetase enzymes (anti-Jo-1, antihistidyl-tRNA, and several others) with overlapping clinical features of myositis, arthritis, and interstitial lung disease.
- Polymyositis/scleroderma (PM/Scl) syndrome is characterized by overlapping features of scleroderma and polymyositis, and PM/Scl antibody, and by the presence of Raynaud phenomenon, tendon inflammation, and interstitial lung disease. Sclerodactyly may occur, but the truncal sclerodermatous skin changes characteristic of systemic sclerosis are absent.

Rigorous epidemiologic studies on the incidence and prevalence of overlap syndromes have not been done, and data are lacking. However, they are all rare conditions. The estimated prevalence of mixed connective tissue disease (MCTD) in a Japanese epidemiologic series was 2.7 per 100,000. Antisynthetase antibodies (including anti-Jo-1 or antihistidyl-tRNA) are found in 5 % to 20 % of patients with polymyositis or dermatomyositis [2].

CASE REPORT

A 71 year old Caucasian female was seeking for medical care. She suffered from dyspnea during minor physical exertion (up to 50 m of quite walking on ground level) and no at rest, dry cough, intermittent wheezing, sensation of obstructed expiration during physical exertion, as well as at rest or at night, chest tightness, and lower extremities edema in the evening predominantly, after night it abates. Additionally she had mouth dryness, difficulty swallowing, pain and sandy sensation in the eyes, dryness of skin, numbness and tingling of the lower limbs, mostly distal parts, and the lateral aspects of the face, muscle weakness, especially during raising the hands up, intermittent joint pain in the knees, shoulders, wrist, ankles, subfebrile fever (up to 37.4°C), photosensitivity, fatigue.

Over 7 years (since 2011) patient suffered from dryness of eyes and mouth, intermittent pain in parotid salivary gland. She was surveyed and treated by rheumatologist about Sjögren Syndrome, moderate level of activity, and received symptomatic treatment (life style modification, artificial tears liberally). During last year the patient noticed numbness and tingling of the lower limbs and face, muscle weakness, rash on eyelids, fatigue, fever, and photosensitivity. Rheumatologist diagnosed dermatomyositis, and prescribed gluco-corticoids 12 mg daily, methotrexate 7.5 mg per week. Her condition was stable, symptoms did not progress. Recent month patient's health worsened, developed severe progressive dyspnea, dry cough.

Her mother suffered from musculoskeletal pain; she was not surveyed and had not precise diagnosis; she used NSAIDs locally to relieve her symptoms. Her brother suffered from skin disease with hyperkeratosis, presumably seborrhea. No family history of hypertension, diabetes mellitus. She had no allergic reactions. She had no history of smoking, alcohol or illicit drug use.

Physical examination revealed following data: Temperature 37,1°C; Pulse 70 bpm; Blood pressure 140/80 mm Hg; Respiratory rate 16 tpm; Height 160 cm; Weight 68 kg; BMI 27.

It was elderly female, which was well oriented to space and time. Her posture was active. It was occurred central type of obesity (waist circumference 112 cm). Skin was pale and dry. Drew attention face and neck erythema – V-sign; eye puffiness; periorbital violaceous erythema – heliotropes rash; hand puffiness; skin of the fingers was dry, rough, with a signs of hyperkeratosis and small fissures – Mechanic's hand, no focal thickening were detected. Conjunctiva was dry and hyperemic, but without fibrin threads and erosions or ulcers, yellowish crusts were at the eyelids. Mucous membranes of the mouth were dry, single erosions occurred. Tongue was dry and bright pink with a multiple fissures. Parotid and submandibular salivary glands were tender to palpation. Bronchial breathing in lungs to auscultation, on basal parts of both lung occur fine crackles. Peripheral pulse was full and regular. JVP + 2 cm. Apex beat was in 5^{th} intercostal space 1 cm to the left of the left midclavicular line and had diminished force. S1 and S2 heart sounds was soft to auscultation, diffuse systolic murmur grade II at all points was detected. Abdomen was increased in size, participated in breathing actively; during palpation was soft and non-tender, hyperpneumatosis occurred, no visceromegaly.

Joints during examination were not changed; passive and active movement was painless. Peripheral muscles were atrophic, tender and dense to palpation, strength of shoulder girdle muscles was diminished, distal muscle strength was preserved. At the time of examination peripheral edema was absent. Stool was daily. Urination mildly decreased (no more than 1000 ml/24h). Unstimulated salivary flow during 15 minutes equals <1 mL.

Laboratory and instrumental methods revealed following data. Complete blood count fell down to normal ranges: RBC $4.56\times10^{12/L}$, Hb 141 g/L, WBC 7.0×10^{9}, thrombocytes 201×10^{9}/L. Urine analysis was without abnormalities: protein and glucose were absent, Leu 1–2/hpf, RBC 2–4/hpf, casts were not detected. Biochemical blood profile revealed high level of creatinekinase 261 U/L (N 26.0–140.0 U/L), AlAT 83 U/L (N < 33.0 U/L), AsAT 45 U/L (N < 32.0 U/L), LDH 296.53 U/L (N 135.0–214.0 U/L), which confirmed presence of myositis. Normal creatinine 87 mkmol/L (N 53.0–97.2 mkmol/L) and urea 3.0 mmol/L (N 2.76–8.07 mmol/L) were detected. Also mild hypokalemia 3.0 mmol/L, hypochloremia 82.3 mmol/L and hypocalcemia 2.13 mmol/L occurred. Rheumatologic profile reflect increased ESR 35 mm/h and RF 37.0 IU/mL (N < 14 IU/mL), and normal C-RP 3.6 mg/L (N < 5.0 mg/L). Patients with dermatomyositis have higher levels of C-reactive protein and erythrocyte sedimentation rate than healthy controls, but these values were not associated with clinical or laboratory parameters of disease activity. However, erythrocyte sedimentation rate may be a valid parameter for screening pulmonary involvement [3]. Immunologic profile represented high titer of ANA 1:3200 (N < 1:100), anti-dsDNA IgG > 300 AI, anti-SS-A IgG > 8 AI, anti-SS-B IgG > 8 AI, > 8 AI. Anti-SS-A IgG and anti-SS-B IgG confirmed presence of Sjögren syndrome; anti-JO-1 IgG – antisynthetase syndrome; anti-dsDNA IgG is associated with systemic lupus erythematosus, but may be present in other rheumatic diseases [4]. PCR detected high titers of IgG to herpes virus infection 6, 5, 3. Viruses may play a part in the pathogenesis of idiopathic autoimmune rheumatic diseases [5]. Also it was revealed subclinical hypothyroidism: TSH 13.38 μU/mL (N0.27-4.2 μU/mL), T4 free 0.88 ng/dL (N 0.93-1.7 ng/dL), and boundary value TPO 31.7 IU/mL (N < 34 IU/mL). Thyroid disease, especially hypothyroidism, is a common autoimmune condition which can be seen more frequently in patients with other autoimmune diseases [6]. Hypothyroidism may be masked by symptoms of dermatomyositis. ECG was low voltage with sinus rhythm, 70 bpm, normal heart axis, ventricular premature contraction, right atrial enlargement (II, III), and violation of repolarization in V5–V6.

Pulmonary function test showed moderate violation of lung ventilation by mixed (obstructive & restrictive) type. Echocardiography revealed hypertrophy and enlargement of both ventricles (LVPW 12.2 mm, VST 12.9 mm, RV EDD 22 mm, RVW 6 mm), signs of pulmonary hypertension, mild pericardial effusion (up to 7 mm), but preserved EF 78 %. To clarify occult malignancy, investigation with aim of tumor screen was made. Abdomen ultrasound was unremarkable. Upper GIT endoscopy represented lower esophageal sphincter failure, GERD 0 stage, duodeno-gastral reflux, and erythematous reflux gastritis. Double-contrast barium enema examination showed descending colitis. Mammography and gynecological examination were unremarkable. Three thyroid nodules in the left lobe and isthmus up to 15×13 mm were detected on thyroid ultrasound.

It should be noted, it was the first time, when pulmonary hypertension was detected in this patient. Cause of this was poorly understood. This fact led to a further search for a reason of pulmonary hypertension and severe progressive dyspnea. Anti-Jo-1 IgG is strongly associated with interstitial lung disease and pulmonary hypertension [7]. On the other hand patients with dermatomyositis has increased incidence of pulmonary thromboembolism [8]. Each of these conditions should be either confirmed or excluded. Blood test for D-dimer disclosed evidence of thrombosis: D-dimer 8.1 μFEU/mL (N < 0.5 μFEU/mL). Coagulogram (prothrombin time, INR, APTT, thrombin time, fibrinogen) was unremarkable. During chest CT-scan in the lower lobe of both lungs detected areas of decreased pneumatisation with indistinct borders – ground glass pattern, up to 45*30 mm in diameter and moderate apical pneumofibrosis. Ground glass opacity is a descriptive term referring to an area of increased attenuation in the lung on computed tomography with preserved bronchial and vascular markings. It is a non-specific sign with a wide etiology including chronic interstitial

disease, infection and acute alveolar disease [9]. CT Pulmonary angiography revealed signs of multiple segmental thromboembolism of the pulmonary artery branches (segmental arteries of 4, 5, 8, 9 segments of the left lung and 4, 6, 9, 10 segments of the right lung).

Taking into account the obtained data, final diagnosis was established. Main: Primary Sjögren's syndrome, moderate. Anti-Jo-1-antisynthetase syndrome. Interstitial lung disease. Non-massive pulmonary thromboembolism. Pulmonary hypertension. Respiratory failure type I. Chronic mild pericarditis associated with rheumatic disease. Heart failure with preserved EF (78 %) II FC NYHA. Concomitant: Autoimmune thyroiditis, hypothyroidism. Moderate GERD. Chronic refluxgastritis. Duodenogastral reflux. Descending colitis.

There are no FDA-approved therapies for the management of any of the overlap syndromes. There is a paucity of data from controlled trials to support management strategies, in which the clinical features and need for treatment are highly variable and tailored to the organ systems involved and the severity of involvement. The overall goal of therapy is symptom control and, where possible, arrest of the underlying autoimmune disease process. Among patients with antisynthetase syndrome and interstitial lung disease, prednisone is the most frequently used therapy, although additional immunosuppressive agents are increasingly being used. Symptomatic treatment included: Methylprednisolone 64 mg daily, Mycopheno-late Mofetil 60 mg daily with following titration with increasing doses, Omeprazole 20 mg in the morning for gastroprotection. Pulmonary embolism management included anticoagulant therapy: Enoxaparin 60 mg bid, Warfarin 5 mg controlled by INR 2-3. Treatment of pulmonary hypertension: Diltiazem-retard 90 mg bid, Sildenafil 5 mg tid. Taking into account that viruses can to trigger autoimmune process, it was necessary to eliminate herpes infection. For the patient was prescribed Acyclovir 400 bid.

PROGNOSIS

The overall outlook is defined by the severity of individual organ involvement. Some patients will have minor symptoms easily controlled with few pharmacologic interventions. Others will have progressive internal organ dysfunction, with the development of life-threatening complications that may or may not be responsive to immunosuppressive therapy [10]. In these patients the onset of pulmonary hypertension, cardiac involvement, or interstitial lung disease each portends a poorer prognosis, and they are indications for aggressive immunosuppressive therapy. Pulmonary hypertension is the commonest disease-related cause of death in patients with overlap syndrome. Patients with antisynthetase syndrome are generally considered to have a poor prognosis, with mortality 3 times greater than that of myositis/dermatomyositis without anti-synthetase syndrome [11].

Plenty of unresolved questions are being studied by scientists including: to determine the origin of chronic and persistent activation of immune system; to explain the role of immunologic, immunogenetic and neuroendocrine factors in the pathogenesis of the disease; to find a specific immune treatment of the disease.

We would like to hope that in the near future for this group of grave diseases adequate management will be developed.

REFERENCES

1. Maddison P. J. Mixed connective tissue disease, overlap syndromes, and eosinophilic fasciitis / Maddison. // Annals of the rheumatic diseases. – 1991. – No. 50 (Supple 4). – P. 887–893.
2. Young L. Overlap syndromes [Electronic resource] / L. Young, C. Lozada // Epocrates. – 2018. – Links: https://online.epocrates.com/diseases/101811/Overlap-syndromes/Key-Highlights.
3. Miossi R. Could C-reactive protein and erythrocyte sedimentation rate support monitoring of dermatomyositis and polymyositis activity? / R. Miossi, F. H. Carlos de Souza, S. K. ShinjoI. // MedicalExpress. – 2017. – No. 4.
4. Firestein G. S. Kelley's textbook of rheumatology / Firestein., 2012. – 2292 p – (Elsiever). – (9).
5. Mechanisms of viral pathogenesis in rheumatic disease. // Annals of the rheumatic diseases. – 1999. – No. 58. – P 454–461.

6. Berman J. R. Undifferentiated connective tissue disease – in-depth overview [Electronic resource] / Jessica Berman – Links://www.hss.edu/conditions_undifferentiated-connective-tissue-disease-overview.asp.
7. Mileti L. M. Clinical characteristics of patients with anti-Jo-1 antibodies / L. M. Mileti, M. E. Strek, T. B. Niewold. // Journal of clinical rheumatology. – 2009. – No. 15. – P. 254–255.
8. Risk of deep venous thrombosis and pulmonary embolism in individuals with polymyositis and dermatomyositis: a general population-based study / E. C.Carruthers, H. K. Choi, E. C. Sayre, J. A. Aviña-Zubieta. // Annals of the rheumatic diseases. – 2016. – No. 75. – P. 110–116.
9. Vanaclocha Y. R. Ground glass opacification [Electronic resource] / Y. R. Vanaclocha, B. Amini – Links: https://radiopaedia.org/articles/ground-glass-opacification-1.
10. Herviera B. Clinical phenotypes and prognosis of antisynthetase syndrome / B. Herviera, O. Benvenisteb. // La Revue de Médecine Interne. – 2014. – No. 35. – P. 453–460.
11. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 french canadian Patients / [Y. Troyanov, I. N. Targoff, J. Tremblay, etc.]. // Medicine. : – 2005. – No. 84. – P. 231–249.

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A CLINICAL CASE OF CROHN'S DISEASE

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The article demonstrates a clinical case of Crohn's disease. The clinical manifestation of the disease, a diagnostic approach based on laboratory and instrumental methods with discussion of obtained results, and the up-to-date methods of investigation based on the literature data are shown. The significance of lifestyle modification, optimal drug treatment and regular check-ups for improvement of prognosis is emphasized.

KEY WORDS: Crohn's disease, inflammatory bowel disease, clinical case

КЛІНІЧНИЙ ВИПАДОК ХВОРОБИ КРОНА

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В статті наведено клінічний випадок хвороби Крона. Показані клінічні прояви захворювання, підхід до діагнозу на підставі лабораторних та інструментальних методів обстеження з обговоренням отриманих результатів та сучасні методи діагностики на підставі даних літератури. Підкреслюється важливість модифікації образу життя, оптимальної медикаментозної терапії та регулярного спостереження за хворим для покращення прогнозу.

КЛЮЧОВІ СЛОВА: хвороба Крона, запальні хвороби кишечнику, клінічний випадок

КЛИНИЧЕСКИЙ СЛУЧАЙ БОЛЕЗНИ КРОНА

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В статье приведен клинический случай болезни Крона. Показаны клинические проявления заболевания, подход к диагнозу на основании лабораторных и инструментальных методов обследования с обсуждением полученных результатов и современные методы диагностики на основании данных литературы. Подчеркивается важность модификации образа жизни, оптимальной медикаментозной терапии и регулярного наблюдения за больным для улучшения прогноза.

КЛЮЧЕВЫЕ СЛОВА: болезнь Крона, воспалительные заболевания кишечника, клинический случай

INTRODUCTION

Crohn's disease (CD) is a kind of the inflammatory bowel disease (IBD).It is an idiopathic chronic process which affects any section of digestive tract and is characterized by inflammation of the lining of the gastrointestinal (GI) tract. The other form of

IBD is called ulcerative colitis (UC), which can cause identical symptoms and is sometimes mistaken for CD. While UC is limited to the mucosal layer of the colon, CD can affect any segment of the GI tract from mouth to anus and is characterized by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation. One of the considerable distinguishing features between CD and UC is that CD can also affect eyes, spine, skin and joints. The most prevalent localization of affection of the GI tract in CD is ileum and colon. CD can often be confused with other conditions such as irritable bowel syndrome, food poisoning, an upset stomach, or an allergy. Early detection and diagnosis can help to avoid severe complications and allow early initiation of treatment. Diagnosis is therefore based on the clinical presentation, physical examination, laboratory and imaging tests (e.g., MRI), endoscopy, and serological testing [1].

CLINICAL CASE

A 54-year old man was admitted to the Institute of Therapy with complaints of diarrhea for 10–15 times per day with blood and mucus mainly at night, fatigue, abdominal cramps, weight loss.

Anamnesis morbi

Patient developed all symptoms five years ago when diarrhea with blood and fatigue occurred. The ulcerative colitis was diagnosed. The patient was prescribed drug treatment with mesalazine with marked efficacy. Further the patient refused treatment and supervision by gastroenterologist. The health status was worsened in October 2017 when lower abdominal pain, diarrhea with blood occurred. The patient was admitted to the Kharkiv Research Institute of General and Emergency Surgery. The colonoscopy showed narrowed lumen of sigmoid colon to 8 mm at a distance of 30 cm from the anus, mucous membrane was loose, edematous, with a lot of ulcers and granulation growths, covered with fibrin and necrotic detritus. Histologically – granulation tissue, necrotic detritus and fragments of the hyperplastic mucosa of the colon with severe chronic inflammatory infiltration. The diagnosis ulcerative colitis, partial large bowel obstruction, chronic anemia was established. The health status was slightly improved. The patient was referred to the Institute of Therapy for the purpose of clarifying the diagnosis and correction of therapy.

Anamnesis vitae

Patient denies tuberculosis, hepatitis, sexually transmitted infections, traumas, hereditary diseases. He has had an acute thrombosis and necrosis of hemorrhoidal nodes. He does not have any surgical intervention. Allergic history is negative. The patient denies smoking and alcohol abuse.

Objective examination

Patient's conciseness is clear, general condition is of moderate severity, posture is active. Patient is orientated in place, time and his personality. He has an asthenic constitution and low nutrient intake. Skin and visible mucous membranes are pale. Thyroid gland is not enlarged. Peripheral lymph nodes are non-palpable. Respiratory rate is 18 per minute. Lung percussion reveals resonant sounds. Vesicular breathing was auscultated. Heart borders are not shifted. Heart auscultation: heart rhythm is regular, heart sounds are muffled. Pulse rate is 83 beats per minute. BP is 100/70 mm Hg on both arms. Abdomen is slightly inflated, participates in breathing. Palpation is painful in the left iliac region. Blumberg sign is negative. Liver and spleen are non-palpable. Pasternatsky's sign is negative on both sides. Ankle edemas are present.

Laboratory and instrumental tests

In ***CBC (03.10.17)*** low levels of erythrocytes ($3{,}09*10^{12}$/L; normal range $4{,}00–5{,}00*10^{12}$/L), hemoglobin (82 g/L; normal range 130–160 g/L); low levels of mean corpuscular hemoglobin concentration (MCHC) (301 g/L, normal range is 310–355 g/L), elevated levels of platelets (539, $5*10^{9}$ l), hematocrit (27,2 %; normal range 35–55 %); normal mean corpuscular volume (MCV) (88,0 fL; normal range 80,0–100,0 fL), normal mean corpuscular hemoglobin (MCH) (26,5 pg; normal rage 26,0–34,0 pg), white blood cells (WBC) are normal $5{,}2*\ 10^{9}$/L (normal range $4{,}0–9{,}0*10^{9}$/L), elevated levels of lymphocytes (48 %) and erythrocytes sedimentation rate (ESR) – 48 mm/h. In CBC the anisocytosis and poikilocytosis are marked.

The possible causes of anemia in CD include intestinal blood loss which can result in iron deficiency anemia; also anemia of chronic disease due to chronic inflammation and megaloblastic anemia secondary to vitamin B12 and folate malabsorption in chronically inflamed ileum may be present. Unlike the other causes, vitamin B12 and folate deficiencies lead to macrocytic anemia [2].

In patient's CBC hypochromic normocytic anemia and features of iron deficient are present.

Inflammatory markers such as elevated ESR, thrombocytosis are also present in CBC.

Urinalysis (03.10.17): no abnormalities were found.

Blood biochemistry (03.10.17): elevated levels of very-low-density lipoproteins (VLDL) (0, 74 mmol/L, normal range is 0, 25–0, 72 mmol/L) and C-reactive protein (CRP) (192 mg/l; normal range is 0–6 mg/l), decreased level of total protein (52 g/l, normal range is 65–85 g/l) and blood albumin (29, 0 %; normal range is 56, 6–66, 8 %); increased levels of alfa-2 globulin (12,4 %; normal range is 6,9–10,5 %), beta globulin (21,2 %; normal range is 7,3–12,5 %) and gamma globulin (34,4 %; normal range is 12,8–19,0 %).

Liver and kidney function tests are unremarkable.

Inflammatory marker such as markedly elevated CRP is present.

Hypoproteinemia and hypoalbuminemia can be attributed to malabsorption. Syndrome of malabsorption which develops due to a malfunction of the intestinal wall or intraluminal disorder (e.g., enzyme deficiency) those results in the insufficient absorption of breakdown products. Malabsorption can affect macronutrients (eg, proteins, carbohydrates, fats), micronutrients (eg, vitamins, minerals), or both. Signs and symptoms depend on the location of the defect and can include diarrhea, steatorrhea, abdominal distention, flatulence, weight loss, anemia, vitamin deficiencies [2].

Coprogram (03.10.17): unformed stool, feces test for latent blood was weakly positive, a large amount of starch grains, a slightly elevated amount of indigestible fiber, leukocytes, erythrocytes, mucus.

Bacteriological examination of stool (04.10.17): Bifidobacterium and lactobacilli were found.

Stool samples are routinely collected in CD patients to test the presence of WBCs, routine pathogens, ova, parasites, and Clostridium difficile toxin to rule out superinfections during relapses and before the initiation of immunomodulatory therapy [3].

Echocardiography (13.10.17): ejection fraction (EF) is 65%. Contractility function is preserved. The heart chambers are not dilated. The walls of the aorta are compacted.

Abdominal ultrasonography (04.10.17): sings of chronic pancreatitis, chronic cholecystitis with bile congestion and sludges.

Video colonoscopy (10.10.17): the examination was available up to the proximal third of the transverse colon. There is a typical endoscopic picture of Crohn's disease with high activity and total lesion of the large intestine. The acute combined hemorrhoids and the acute anal fissure are present.

Endoscopy confirms the diagnosis, assesses the extent of the disease, helps to differentiate CD from other diseases (e.g., UC, peptic ulcers, etc.), and may also be used as a therapeutic tool (e.g., dilatation of ducts, intestinal loops).

Typical findings of ileocolonoscopy include segmental/discontinuous pattern of involvement. Macroscopic findings specific for CD are the following: linear ulcers (snail trails); other aphthous hemorrhagic mucosa defects (pinpoint lesions); cobblestone sign (characteristic appearance of the mucosa is inflamed sections followed by deep ulcerations that resemble uneven cobblestones); fissures and fistulas. Erythema and transmural inflammation are also present [2].

Computer tomography (CT) of thoracic, abdomen organs and retroperitoneal space with contrasting (05.10.17): The CT data for the neoplastic process are not revealed. The changes in the intestine are probably due to colitis. A concrement of the left kidney is present. Cardiomegaly and small hydropericardium are found.

Kidney stones and gallstones (bile sludge in our patient) can be contributed to such specific intestinal manifestation as disturbed reabsorption of bile acids and bile acid malabsorption. Bile acids emulgate fat and

therefore help in the digestion of fats. If their enterohepatic circulation is disturbed by faulty reabsorption, the liver reacts by producing more bile acids from cholesterol. If this mechanism is exhausted (decompensated bile acid malabsorption), the lack of bile acids results in diarrhea, steatorrhea, deficiencies in fat-soluble vitamins and gallstones and kidney stone formation. Mechanism of gallstones increasingly is related to the loss of the emulgator bile acid. As a result, the cholesterol cannot be dissolved sufficiently and precipitates. Mechanism of kidney stone formation is related to the disrupted creation of calcium oxalate due to an excess of free fatty acids caused by a deficiency in bile acids. Calcium preferably binds to the free fatty acids, leading to increased absorption of free oxalate and a higher risk of kidney stones. Normally, oxalate and calcium combine in the intestines to form an insoluble salt (calcium oxalate) that is excreted in the feces [2].

ECG (13.10.17): sinus rhythm with heart rate 75 beats per minute, left and right ventricular hypertrophy with severe left ventricular overload. Left anterior fascicular block.

Consultation of cardiologist (13.10.17): Essential arterial hypertension II stage, 1st degree, low total cardiovascular risk.

Additional methods of investigation which may be ordered

Serum levels of iron, total iron binding capacity, transferrin, ferritin, vitamin B12 and folate can be used for clarification of the type anemia and evaluation of malnutrition and some nutrient deficiencies.

Anti-Saccharomyces cerevisiae antibodies are antibodies directed at components of the cell wall of the yeast Saccharomyces cerevisiae. The presence of these antibodies is associated with chronic inflammatory bowel disease, most strongly CD [4–5].

Possible detection of fecal calprotectin and/or lactoferrin. Lactoferrin and fecal calprotectin are neutrophil-derived proteins which are used as specific surrogate markers of intestinal inflammation. Lactotransferrin is an iron-binding protein produced by neutrophils and found in secretory fluids and mucosal barriers that inhibits microbial growth. These parameters are commonly used to differentiate between CD and other non-infectious causes of gastrointestinal disorders. In addition, they are used to monitor the course of the disease or to confirm recurrent episodes. These fecal biomarkers may help avoid the need for otherwise invasive measures that assess intestinal inflammation [6].

Esophagogastroduodenoscopy also should be considered to assess the possible involvement of the esophagus, stomach, and duodenum and is useful in differential diagnosis between CD and UC. Findings specific for upper GI tract affection in CD include aphthae on mucosa [7].

Differential diagnoses

UC
Infectious gastroenteritis
Irritable bowel syndrome
Colorectal malignancy
Diverticulitis
Non-infectious colitis (post-radiation, drug-induced, ischemic etc.)
Gastrointestinal tuberculosis
Acute appendicitis

Clinical diagnosis

Crohn's disease of the colon, stenosing form with high activity, hormone-dependent, with extraintestinal manifestations (chronic pancreatitis with exocrine insufficiency, chronic cholecystitis with hypokinetic dyskinesia of the gallbladder, biliary sludge). Left kidney stone. Anemia of chronic disease, moderate severity

Essential arterial hypertension II stage, 1st degree, low total cardiovascular risk. HF II FC

Treatment

General approach includes smoking cessation; lactose-free diet in case of secondary lactose intolerance which is present in approximately one third of cases; in the case of malabsorption syndrome appropriate replacement of vitamins, calories, protein, zinc, calcium and other nutrients is considered. Treatment bile acid diarrhea includes administration of ion-exchange resins to bind bile acids (e.g., cholestyramine).

During acute episodes recommendations to avoid dietary fibers should be given and parenteral nutrition can be prescribed.

Our patient received drug therapy: reosorbilact solution 200,0 ml during four

days, then infesol solution 500,0 ml and 5 % glucose solution with ascorbic acid 4,0 ml during three days, 20 % human albumin solution 100,0 ml one day, methyl-prednisolone 32 mg/day during first seven days then dose was reduced to 28 mg/day, mesalazine 300 mg/day, enalapril 10 mg/day, hydrochlorothiazide 12,5 mg/day Patient condition was improved: the frequency of defecations was decreased, blood in feces disappeared. Nevertheless fatigue and ankle edemas were still present.

After discharge patient received recommendation to follow-up low-fiber, low-fat and low-lactose diet and take plenty of water. Drug therapy includes methylprednisolone 28 mg/day 2 weeks then weekly dose reduction by 4 mg. mesalazine 800 mg 4 times per day, enalapril 10 mg/day, hydrochlorothiazide 12,5 mg/day.

Check-ups

Clinical curse of CD is associated with significantly increased risk of colorectal carcinoma and/or frequent relapses of the disease, that's why close following-up with regular endoscopy is of great importance.

Prognosis

Because the entire gastrointestinal tract is typically affected in CD, it is non-curable disease. The goal of treatment of CD is thus to slow the progression of the disease, avoid recurrence of inflammatory episodes and prevent complications which are extremely common in the absence of optimal treatment. Life expectancy is normal and quality of life may be satisfactory with aggressive evidence-based treatment. Majority of patients (approximately 70 %) requires surgical operations due to complications within 15 years of their onset [7].

REFERENCES

1. Fakhoury M. Inflammatory bowel disease: clinical aspects and treatments / M. Fakhoury, R. Negrulj, A. Mooranian, H. Al-Salami // Journal of Inflammation Research. – 2014. – No. 7. – p. 113–120.
2. Ha F. Crohn's disease: a clinical update / F. Ha, H. Khalil // Therap. Adv. Gastroenterol. – 2015. – No 8(6). – p. 352–359.
3. Takeuchi K. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease / K. Takeuchi, S. Smale, P. Premchand, et al.] // Clin Gastroenterol Hepatol. – 2006. – No 4(2). – p. 196–202.
4. Cambridge G. Anti-neutrophil antibodies in inflammatory bowel disease: prevalence and diagnostic role /G. Cambridge, D. S. Rampton, T. R. J. Stevens et al] // Gut. - 1992. – No 33(5). – p. 668–674.
5. Lecis P. p-ANCA and ASCA antibodies in the differential diagnosis between ulcerative rectocolitis and Crohn's disease / P. Lecis, B. Germanà, N. Papa et al] // Recenti progressi in medicina. – 2002. – No 93(5). – p. 308–313.
6. Di Ruscio M. Surrogate Fecal Biomarkers in Inflammatory Bowel Disease: Rivals or Complementary Tools of Fecal Calprotectin? // M. Di Ruscio, F. Vernia, A. Ciccone et al.] // Inflamm. Bowel. Dis. – 2017. – No 24(1). – p. 78–92.
7. Al-Bawardy B. Endoscopic and Radiographic Assessment of Crohn's Disease / B. Al-Beardy, S. L. Hansel, J. L. Fiddler, et al.] // Gastroenterol Clin North Am. – 2017. – No 46(3). – p. 493–513.

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RADIOFREQUENCY ABLATION IN ATRIAL TACHYCARDIA PAROXYSM ON EXAMPLE OF CLINICAL CASE

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The disappearance of atrial tachycardia paroxysms after radiofrequency catheter ablation (RFA) of ectopic focus in a left atrium is presented on example of clinical case. Atrial tachycardia paroxysms disappeared after ablation completely.

KEY WORDS: atrial tachycardia paroxysms, radiofrequency catheter ablation

РАДІОЧАСТОТНА АБЛЯЦІЯ ПРИ ПАРОКСИЗМІ ПЕРЕДСЕРДНОЇ ТАХІКАРДІЇ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Зникнення нападів передсердної тахікардії після виконання радіочастотної катетерної абляції (РЧА) ектопічного вогнища у лівому передсерді на прикладі клінічного випадку. Нападки передсердної тахікардії після абляції зникли зовсім.

КЛЮЧОВІ СЛОВА: напади передсердної тахікардії, радіочастотна катетерна абляція

РАДИОЧАСТОТНАЯ АБЛЯЦИЯ ПРИ ПАРОКСИЗМЕ ПРЕДСЕРДНОЙ ТАХИКАРДИИ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Исчезновение приступов предсердной тахикардии после проведения радиочастотной катетерной абляции (РЧА) эктопического очага в левом предсердии на примере клинического случая. Приступы предсердной тахикардии после абляции исчезли полностью.

КЛЮЧЕВЫЕ СЛОВА: приступы предсердной тахикардии, радиочастотная катетерная абляция

INTRODUCTION

Atrial tachycardia accounts for approximately 20 % of all supraventricular tachycardia [1]. Heart ablation is based on duplication or destruction of those tissues that provoke an irregular heartbeat [1–3]. Heart ablation is the most effective method of treatment, if the previous pharmacotherapy was not effective or it cannot be used due to side effects in the body [1–4].

Taking this into account, we present a clinical case that demonstrates the disappearance of atrial tachycardia paroxysms after radiofrequency catheter ablation (RFA).

CLINICAL CASE

54 years old woman, a resident of Donetsk region. Diagnosis during hospitalization: Permanent-recurring atrial tachycardia.

Complaints: shortness of breath, palpitation, diffuse headaches in a high blood pressure periods, dizziness, general weakness.

Anamnesis morbi: patient suffers from hypertension for about 10 years (maximal blood pressure (BP) = 160/90 mm Hg). During the same time, heartbeat attacks, provoked by stress, nearly 1 time in 6 months, initially stopped independently during rest. Last 2 years heartbeat attacks became more frequent (every 3 months), which were stopped by anti-arrhythmic drugs. On electrocardiogram (ECG) a supraventricular tachycardia with narrow QRS complexes, with rate of 140–160 per minute, P is not differentiated.

Medicinal therapy (regular cardiomagnil, irregularly bisoprolol) without effect. RFA intervention is recommended. Anamnesis vitae: carried diseases: angina in childhood, occasionally catarrhal diseases. Family history: patient notes hypertension and atrial fibrillation in her mother. She denies harmful habits. Tuberculosis, viral hepatitis, diabetes mellitus, sexually transmitted diseases, transfusion transmissibility is denied. Operations and injuries are denied too. Allergic history without peculiarities.

Objective status: general condition of moderate severity, consciousness is clear, position is active. Skin and visible mucous membranes are clean, pale pink. Thyroid gland: palpable isthmus. Mammary glands are symmetrical, without seals. Musculoskeletal system without peculiarities. There is pulmonary sound above the lungs, vesicular breathing, no crackles. The pulsation of neck vessels is not determined. Heart borders are within the normal range. Heart beats are rhythmic, the tones are muffled, I > II at the apex, on the basis of no accents, murmurs are not heeded, heart rate – 66 beats/min. BP (right arm) = 130/80 mm Hg; BP (left arm) = 125/80 mm Hg. The tongue is clean and moist. Belly palpation is soft, painless. The liver border is at arch edge, the spleen is not palpable. Pasternatsky's symptom is negative on both sides. Peripheral edema is absent.Tests results: in CBC, urine and biochemical blood test without changes. ECG (January 31, 2017) before RFA: paroxysm of atrial tachycardia with heart rate 150 per min, vertical position of electric heart axis, left ventricular (LV) hypertrophy; ECG after RFA (01.02.2017) – sinus rhythm, regular, with heart rate 72 per min, vertical position of electrical heart axis, LV hypertrophy. Holter monitoring before RFA: for monitoring time 23:54 rhythm disturbances were registrated – chronic permanent-recurring atrial tachycardia with short episodes of sinus rhythm, mainly at night with an average heart rate of 104 per min; minimal heart rate – 60 per min at 03:28 – during sleep, maximal heart rate – 192 per min at 06:56 – during exercise. The circadian index is 1.46 (elevated). At echocardiography (Echo) (January 31, 2017): aorta and valves closure, mitral valve regurgitation of 1 degree, heart chambers are not dilated. The LV walls are not thickened. The LV systolic function satisfactory during severe tachycardia. Zones of local contractility violations are not localized. Right chambers are not dilated. Tricuspid regurgitation of 1 degree, ejection fraction (EF) – 61 %. Heart rate variability (HRV) was recorded at sinus rhythm before RFA (01.02.2017), it reflected the high total power (TP) of spectrum, and after RFA TP decreased by 5 times, but remains high, it indicating a slow humoral and metabolic type of regulation. 02.01.2017 RFA was performed – complete isolation of ectopic zone in the left atrium was performed. Clinical diagnosis: coronary artery disease: diffuse cardiosclerosis. Atrial recurrent tachycardia with successful ablation, with the disappearance of tachycardia paroxysms and restoration of cardiac rhythm. Arterial hypertension II st. 1 degree, cardiovascular risk is low. Heart failure I st., I functional class (FC) with preserved systolic function of LV. Our recommendations: cardiologist observation at the place of residence. Bisoprolol 5 mg per day, in the morning, under the control of heart rate. Cardiomagnil 75 mg per day, before sleeping for a long time. Phone visit (02.03.17): patient lives at the far distance from our center, which makes it impossible for her physical visit. A month later, after an RFA, patient reported heart rhythm disturbances, which were twice a month, lasted about 15-20 minutes and stopped at rest. The patient takes bisoprolol 5 mg/day and cardiomagnil 75 mg/day. Epilogue: at the moment when the article was completed, during the second telephone visit (04.04.17), patient did not mention disturbances of heart rhythm. Patient was advised to take bisoprolol 10 mg/day. It is noted in literature that in acute postablative period there are possible rhythm disturbances with future recovery [5–6].

CONCLUSIONS

In this case, the RFA of atrial tachycardia was effective. The initial high total power of the HRV spectrum in the patient after ablation

decreased by 5 times, but may predict rhythm disturbances in future. In pharmacotherapy, which included cardiomagnil and bisoprolol, the reduction in HRV suggested a gradual increase of the bisoprolol dose.

REFERENCES

1. Regular atrial tachycardia following pulmonary vein isolation for paroxysmal atrial fibrillation: a retrospective comparison between the cryoballoon and conventional focal tip radiofrequency techniques / [J. I. Juliá, G. B. Chierchia, C. de Asmundis et al]. // J Interv Card Electrophysiol. – 2015. – No. 42. – P. 161–166.
2. Revishvili A. W. Hiryrgicheckyye i interventancionnyye podchodu k lecheniu ektopicheskoi predserdnoi tachikardii / A. W. Revishvili, G. S. Rashbaeva, S. Y. Serguladze. // Vestnik aritmologii. – 2011. – No. 6. – P. 53–55.
3. Yabluchanskiy M. I. Internal diseases: the time of global somatic risk / M. I. Yabluchanskiy, A. M. Yabluchanskiy, O. Y. Bychkova. // The Journal of V. N. Karazin Kharkiv National University. – 2013. – No. 25. – P. 5–7.
4. Very long-term results of atrial fibrillation ablation confirm that this therapy is really effective / C.Tutuianu, J. Szilagy, R. Pap, L. Saghy. // J Atr Fibrillation. – 2015. – No. 8. – P. 1226.
5. Scheinman M. M. Patterns of catheter ablation practice in the United States / Scheinman. // Pacing Clin. Electrophysiol. – 1994. – No. 17. – P. 873–877.
6. Catheter ablation of atrial fibrillation in U.S. Community practice—results from outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) / [F. Holmqvist, D. J. Simon, B. A. Steinberg та ін.]. // J Am Heart Assoc. – 2015. – No. 4. – P. e001901.

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CLINICAL AND CHEST X-RAY FEATURES OF PNEUMONIA IN INJECTING-DRUG USERS

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On an example of a clinical case in a patient with drug addiction, the reviewed clinical and chest X-ray features of community-acquired pneumonia, the diagnostic algorithms and the differential diagnostics are based on the recommendations of the Ukrainian Association of Pulmonology. The treatment strategy of the patient in the conditions of an ambulatory are described.

KEY WORDS: community-acquired pneumonia, injecting drug use, diagnosis, treatment strategy

КЛІНІКО-РЕНТГЕНОЛОГІЧНІ ОСОБЛИВОСТІ ПНЕВМОНІЇ ПРИ ІН'ЄКЦІЙНІЙ НАРКОМАНІЇ

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На прикладі клінічного випадку у пацієнта з наркозалежністю розглянуто клініко-рентгенологічні особливості негоспітальної пневмонії, алгоритми діагностики та диференційної діагностики, які засновані на рекомендаціях української асоціації пульмонологів. Описана тактика ведення пацієнта в умовах поліклініки.

КЛЮЧОВІ СЛОВА: негоспітальна пневмонія, ін'єкційна наркоманія, діагностика, тактика ведення

КЛИНИКО-РЕНТГЕНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ПНЕВМОНИИ ПРИ ИНЪЕКЦИОННОЙ НАРКОМАНИИ

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На примере клинического случая у пациента с наркозависимостью рассмотрено клинико-рентгенологические особенности внебольничной пневмонии, алгоритмы диагностики и дифференциальной диагностики, которые основаны на рекомендациях украинской ассоциации пульмонологов. Описанная тактика ведения пациента в условиях поликлиники.

КЛЮЧЕВЫЕ СЛОВА: внебольничная пневмония, инъекционная наркомания, диагностика, тактика ведения

INTRODUCTION

According to statistical data, pneumonia ranks first among the causes of death from infectious diseases, the sixth among all causes of death and the fourth among causes of death in patients older than 65 years [1–2].

According to the National Report for 2017 on the Drug Situation in Ukraine in 2016, about three million people (about 14 % of the population of Ukraine) are drug addicts [3].

Therefore, particular importance today is given to the problem of so-called «syringe» infections, among which the most frequent infections are HIV, viral hepatitis B and C, bacterial hematogenous infections that cause serious complications: pneumonia, septicemia, bacterial endocarditis [3].

With intravenous drug addiction, after non-sterile and usually unsuccessful attempts to gain access to peripheral veins, proximal and central veins are used to inject the drug, which leads to

a rapid spread and deeper penetration of bacterial agents into the human body [4].

In persons who use drugs intravenously, most often an infection is caused by Golden Staph (Staphylococcus aureus) [5]. This can be explained by the fact that 25–40 % of the population is permanent carriers of this bacterium, which is stored on the skin [5] and with intravenous interventions (procedures) the bacteria enters the systemic circulation.

Thus, drug users, even without immunedeficiency, experience pneumonia of staphylococcal etiology, which is characterized by resistance to antibiotic therapy, severe course, rapid progression, frequent complications and high lethality [6–7].

MATERIALS AND METHODS

In the Kharkiv city ambulatory No. 24 a therapist examined a 37-year-old man. The doctor interviewed the patient, collected anamnesis of the disease and life (medical history), objectively examined the patient then he immediately conducted a clinical and laboratory (clinical analysis of blood, urine) and instrumental (chest X-ray) examination. The diagnosis and healthcare strategy were based on the recommendations of decree No. 128 of the Ministry of Health of Ukraine dated March 19, 2007 «On the approval of clinical protocols for the provision of medical care in the «Pulmonology» specialty» [8].

OBJECTIVES

To consider on an example of a clinical case the diagnostic features and tactics of management of a patient with pneumonia with a background of drug-injecting addiction in conditions of an ambulatory.

RESULTS AND DISCUSSION

A man 37 years, old was admitted to the Kharkiv city ambulatory No. 24 with complaints of a persistent wet cough of yellow-green viscous sputum, dyspnea at rest (shortness of breath), pain in the lower right part of the chest, worse with inspiration, increased sweating combined with chills, general weakness. He was ill for 10 days, when after hypothermia, a dry cough appeared, the body temperature increased to 37.80°C. He started self-treated, he took paracetamol 500 mg 3 times a day, 1 glass of herbal infusion «No. 2» glass 2–3 times a day. The last 3 days he took amoxicillin 500 mg 3 times a day. The state of his health worsened so he came to the therapist. From the anamnesis of life – has been injecting drugs for about 5 years. Objectively: severe bad health condition, temperature of the body – 40°C, paleness and increased moisture of the skin. Percutally dull pulmonary sound below the 5 intercostal spaces to the right of the paravertebral to the middle axillary line and below the 4 intercostal spaces from the middle axillary line to the right parasternal line, where auscultatory breathing was not determined. Over the remaining areas of the lungs a rigid breathing with prolonged exhalation and single small «bubbly» wheeze heard. The respiratory rate is 30/min., auscultation of the heart- deaf tones were determined. Heart rate – 110 beats per minute. Blood pressure – 90/65 mm Hg.

Recommended examination according to the following plan: a clinical blood test, a clinical urine analysis, a biochemical blood test (CRP, total protein and its fractions), a blood test for HIV, a clinical sputum analysis + the presence of mycobacterium tuberculosis, a bacterial sputum culture + detection of sensitivity to antibiotics, chest x-ray, spirography.

In the conditions of the ambulatory. The results of the medical examination were obtained: in the blood count test – leukocytosis (16.7 g/l), accelerated ESR (29 mm/h). On chest radiography: in both of the lung cavities all over there are multiple cavity formations of various sizes in diameter (from 0.5 to 3 cm) with the presence of insignificant liquid levels. On the right at the level of 4–12 ribs and in the sinus is a shading of medium intensity, a homogeneous structure with an oblique fuzzy contour. Conclusion: bilateral abscessed pneumonia complicated by pleurisy to the right. Multiple abscesses of the lungs (Fig. 1).

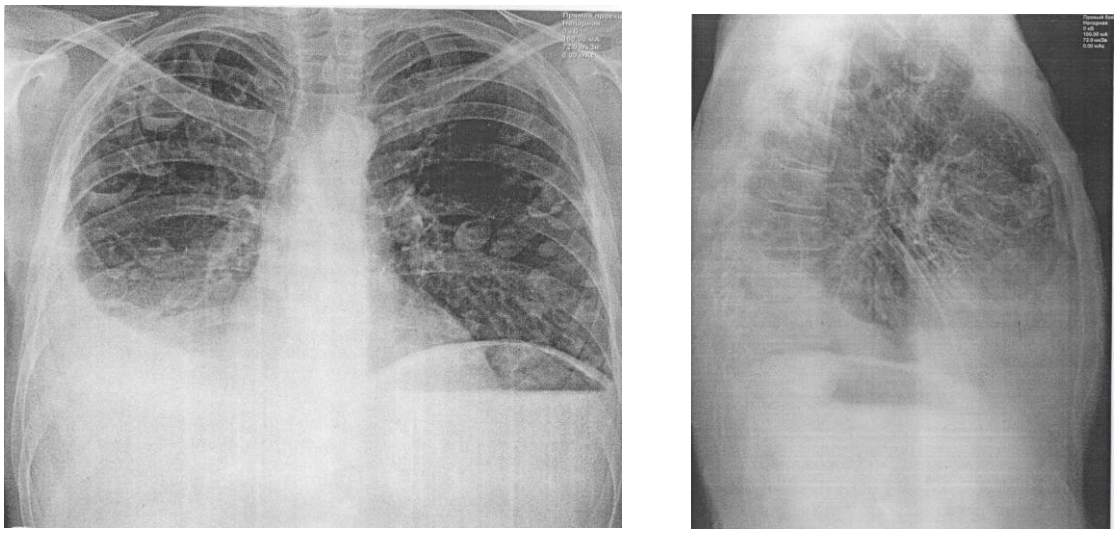

Fig. 1 Chest X-ray in the frontal and lateral projections

The main diagnosis: acquired bilateral abscessing pneumonia, IV clinical group. Multiple abscesses of the lungs. Pulmonary insufficiency III degree.

Complications: right-sided exudative pleurisy.

Concomitant diagnosis: injecting-drug addiction.

Since the patient came to the doctor after self-treatment, it was necessary to evaluate its effectiveness. The determination of the ineffectiveness of antibiotic therapy is carried out 48–72 hours after the start of the drug and is based on the following criteria:

- Preservation or intensification of fever, clinical symptoms, intoxication (Our patient has it);
- Appearance or persistence of hemodynamic instability (Our patient has it);
- Development or enhancement of respiratory failure (Our patient has it);
- There is a need for artificial ventilation (Our patient does not require it);
- Negative chest X-ray picture of the chest (Our patient has it).

In accordance with the algorithm for assessing the effectiveness of antibiotic therapy: the use of amoxicillin (500 mg 3 times a day) in our patient was ineffective.

Since the spectrum of microbial flora in patients of the IV clinical group is diverse (Legionella spp., H. Influenza, Gram-negative enterobacteria, S. Aureus, S. Pneumoniae, M. Pneumonia, in the presence of modifying factors, the pathogen of pneumonia may be P. aeruginosa), it is necessary to consider the features the course of pneumonia, depending on specific pathogens [6]:

- Legionellosis pneumonia, as a rule, occurs in persons visiting rooms with air conditioners, swimming pools and showers. It's characterized by severe course (tendency), diarrhea, neurological symptoms, hepatic dysfunction;
- A pneumonia which is caused hemophilia often occurs in people suffering from chronic bronchopulmonary diseases and alcoholism, is characterized by severe course, discharge of thick sputum with blood, large infiltrates, the probability of getting abscess;
- Staphylococcal pneumonia has an acute onset, severe course (tendency), limited infiltrates (pocket), frequent abscesses and resistance to a group of penicillin's;
- Pneumococcal pneumonia is characterized by acute onset, severe course (tendency), severe fever, prevalence of infiltrates and good response to penicillin antibiotics;
- Mycoplasma pneumonia develops in young patients, it has an acute onset, mild to moderate-course (tendency), catarrhal inflammation of the upper respiratory tract (runny nose, sore throat), cough with scant sputum.

Thus, we can assume that our patient develops staphylococcal pneumonia.

The choice of patient treatment location is determined depending on the evaluation of the severity of pneumonia according to certain criteria.

The «small» criteria include:

- Respiratory rate ≥ 30 in 1 min. (Our patient has it),
- impaired consciousness (Our patient does not have it),
- SaO2 < 90 % (Not determined in our patient),
- The partial pressure of oxygen in the arterial blood (PaO2) is below 60 mm Hg. (Not determined in our patient).
- Systolic blood pressure < 90 mm Hg (Our patient has it)
- Bilateral or multiple lung damage, cavity decay, pleural effusions (Our patient has it).

To «large» criteria of a heavy current of pneumonia carry:

- The need for artificial ventilation (Our patient does not need it),
- Rapid progress of focal-infiltrative changes in the lungs (increase in infiltration rates by more than 50 % within the next 2 days) (Our patient does not have it),
- Septic shock or the need for vasopressor ≥ 4 g (our patient does not have it),
- Acute renal failure of the lungs (Our patient does not have it).

The severe course of pneumonia which matches to ≥ 2 articles from the «small» criteria or 1 article from the «large» criteria, requires the urgent hospitalization of patients in the intensive care unit (ICU). Our patient has a severe course of acquired pneumonia (3 small criteria), so he must be urgently hospitalized in the ICU.

To summarize: the acute onset, severe course, the presence of limited infiltrates and abscesses on the chest x-ray, resistance to the penicillin group hypothetically correspond to the staphylococcal etiology of pneumonia, which is confirmed in the spectrum of microflora in the patients of the IV clinical group, where one of the possible causative agents is S. aureus. The patient has three articles from «small» criteria for the severe course of pneumonia, respiratory rate ≥ 30 in 1 min., Systolic blood pressure < 90 mm Hg, multiple lung damage with decay cavities and hydrothorax, which was an indication for hospitalization in the intensive care unit and intensive care. Also, the presence of fluid in the pleural cavity requires the use of instrumental methods of diagnosis and treatment in conditions of the thoracic surgery department.

Based on the above, the patient was urgently hospitalized in the intensive care unit of the Department of Thoracic Surgery with the help of an ambulance brigade.

CONCLUSIONS

1. Community-Acquired pneumonia acquired by intravenous drug use is characterized by a severe course, febrile body temperature, severe specific lung disease.
2. On the example of this clinical case, the importance of express diagnostics of pneumonia at the ambulatory stage was confirmed to determine the correct tactics of patient management.

REFERENCES

1. WHO. URL: http://www.who.int/mediacentre/factsheets/fs310/en/index.html (Last accessed: 17.03.2018).
2. Linnik M. I., Nedospasova O. P., Tarasenko O. R., Kapustyak V. I., Bushura I. B., Nikiforova L. G. Comparative data on the prevalence of respiratory diseases and medical care for patients with pulmonologic and allergic diseases in Ukraine for 2010–2016. Kiev: Lira-K, 2017. 48p.
3. National report for 2017 on the narcotic situation in Ukraine (according to 2016). URL: http://www.ummcda.org.ua/index.php/86-natsionalnij-zvit-za-2017-rik-shchodo-narkotichnoji-situatsiji-v-ukrajini-za-danimi-2016- hand (Last accessed: 17.03.2018).
4. Holbaev S. A. Features of the course and treatment of postinjectional gonya-inflammatory and vascular complications in patients suffering from drug addiction: The dissertation for a scientific degree candidate of medical sciences: K737.005.03 / Tajik State Medical University. Dushanbe, 2012. 100p.

5. Tong S. Y., Davis J. S., Eichenberger E., Netherlands T. L., Fowler V. G. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clinical Microbiology Reviews, 2015. No. 28 (3). P. 603–661.
6. Feshchenko Yu. I., Golubovskaya O. A., Goncharov K. A. and others. Unresponsive pneumonia in adults: etiology, pathogenesis, classification, diagnostics, antibiotic therapy. Ukrainian pulmonology journal. 2012. No. 4. P. 5–17.
7. Landyshev Yu. S., Goborov N. D., Tsukanova G. D. Infectious complications in chronic dezororfine drug addiction. Amur Medical Journal. 2017. No. 1 (17). P. 76–81.
8. Order of the Ministry of Health of Ukraine No. 128 dated 19.03.2007. On approval of Clinical Protocols for the Provision of Medical Aid in the Specialty «Pulmonology». 21 p.

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ATRIAL FIBRILLATION IN PATIENT WITH DIABETES MELLITUS 2 TYPE: CO-EXISTANCE AND THERAPEUTIC APROCHES

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On the example of the clinical case of atrial fibrillation in patient with diabetes mellitus type 2, were discussed molecular mechanisms and therapeutic perspectives, anticoagulation treatment and anti-arrhythmic treatment strategies benefit. Recommendations on lifestyle modification and medicament treatment tactics are described.

KEY WORDS: diabetes mellitus, atrial fibrillation, anticoagulation, correlation

ФИБРІЛЯЦІЯ ПЕРЕДСЕРДЬ У ХВОРОГО НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ: СПІВІСНУВАННЯ ТА ТЕРАПЕВТИЧНІ МОЖЛИВОСТІ

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На прикладі клінічного випадку вперше діагностованої миготливої аритмії у хворого на цукрово1 діабет 2 типу обговорили молекулярні механізми та терапевтичні перспективи антикоагулянтної терапії та стратегії антиаритмічної терапії. Описано рекомендації з модифікації способу життя і тактики лікування.

КЛЮЧОВІ СЛОВА: цукровий діабет, миготлива аритмія, антикоагулянтна терапія, кореляція

ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ У ПАЦИЕНТА С САХАРНЫМ ДИАБЕТОМ 2 ТИПА: СОСУЩЕСТВОВАНИЕ И ТЕРАПЕВТИЧЕСКИЕ ВОЗМОЖНОСТИ

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На примере клинического случая впервые диагностированной фибрилляции предсердий у пациента с сахарным диабетом 2 типа обсудили молекулярные механизмы и терапевтические перспективы антикоагулянтной терапии и стратегии антиаритмической терапии. Описаны рекомендации по модификации образа жизни и тактике лечения.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет, мерцательная аритмия, антикоагулянтная терапия, корреляция

INTRODUCTION

One of the most frequent cardiac arrhythmias in therapeutic practice is atrial fibrillation (AF). This type of arrhythmias is associated with increased cardiovascular and cerebrovascular complication's risk and mortality. Despite, the relationship between diabetes and AF is unclear [1], nowadays medical world focuses mostly on increased risk of thromboembolic events in patients with co-existed AF and DM but there are significant evidences of an increased AF prevalence in patients with diabetes. Insulin resistance, impaired glucose tolerance, immunity alternations with hypercoagulability, increased angiogenesis and extracellular matrix turnover in patients with diabetes mellitus (DM) as a result will lead to possible endothelial dysfunction, abnormal activation of the reninangiotensin-aldosterone system and pathological atherogenesis , as AF appearance

factors [2]. Also the mail triggers in AF occurrence can be remodeling of the left atrium, atrial dilatation and interstitial fibrosis seen in patients with diabetes [3]. Some studies in patients with diabetes and impaired glucose tolerance with treatment approach of radiofrequency ablation for paroxysmal AF have shown significantly decreased right and left atria voltages due to atrial electrical remodeling and atrial fibrosis [4]. The influence of diabetes on the autonomic nervous system – sympathetic and parasym-pathetic – leads to increased uptake choline and release acetylcholine with shortened atrial effective refractory period and increased dispersion [5–6]. Not all authors are agreeing with this hypothesis. Thus, Frost et al. found any difference in AF rate between diabetic men and women, whereas other ones (Benjamin et al., Nichols et al.) revealed greater risk of AF in women with DM than in male population. In Ruigomez et al. study with 1035 DM + AF patients comparing with 5000 non-diabetic patients with AF were found no association between DM and AF occurrence. A large meta-analysis made in 2011 patients with diabetes had a nearly 40 % greater risk of AF comparing to non-diabetic patients (relative risk 1.39, 95 % confidence interval [CI] 1.10–1.75; $P < 0.001$) [1]. So influence of DM on AF occurrence and re-occurrence after cardioversion is still a matter of discussion.

CLINICAL CASE

A 78-year old female was admitted by ambulance in the emergency department of 5 Kharkiv clinical hospital with complains on palpitation, episodic pressing pain in left part of chest, no clear connection with provoking factors; dyspnea on mild physical exertion and labile blood pressure.

ANAMNESIS MORBI

Patient has a 2-year history of arterial hypertension and atrial fibrillation with an average blood pressure (BP) level of 170/100 mm Hg, which was unsuccessfully ambulatory treated with amiodarone, digoxin, aspirin, spironolactone, and Lisinopril. Hyperglycemia for several years without specific treatment. She was admitted to the hospital following deterioration in her health due to unsuccessful previous therapy.

ANAMNESIS VITAE

Childhood infections, injuries, tuberculosis, sexually transmitted diseases were denied by patient. Hereditary diseases are not identified. Allergic history is burdened (allergic dermatitis for digoxin).Smoking – denied, not an alcohol abuser. Family history of DM and cardio-vascular disease: mother had DM and AH.

OBJECTIVE EXAMINATION

Consciousness: clear; state: moderate severity; body position: active. Temperature: 36.7°C. Patient can orientate herself in place, time and personality. Moves with a walker only. Appearance: pale skin, acrocyanosis**.** Thyroid gland: within normal limits. Musculoskeletal: deformation of hip and knee joints, patient can only walk with support. Obesity II degree (BMI – 35.0). Respiratory rate – 22/min. Lung percussion: no clinically significant changes, resonance. Lung auscultation: weakened breathing in the lower parts of both lungs. Pulse: arrhythmic, 90 bpm; BP – 160/80 mm Hg. Borders of the heart: left border is displaced 2 cm outwards from the left mid clavicular line. Heart auscultation: heart rate (HR) – 97/min, arrhythmic, atrial fibrillation. Muffled heart tones, accentuation of the second tone on the pulmonary trunk point of auscultation, diffuse systolic murmur in all points with epicenter at the apex of the heart. Abdomen: soft and painless, enlarged due to deposition of adipose tissue. Liver: near the rib edge, no pain on palpation of the right hypochondriac region. Spleen: not palpated. Pasternatsky symptom: negative on both sides. Stool and diuresis: normal. Bilateral pitting edema of lower extremities

LABORATORY AND INSTRUMENTALTESTS

Complete blood count data showed: high levels of hemoglobin (152 g/l within the normal ranges120–140), red blood cells (5,06 within the normal ranges $3.9–4.7*10^9$/l) and hemato-crit (43 % within the normal ranges 34–42 %).

Urinalysis: microalbuminuria (0.03 g/l), hematuria as signs of diabetic nephropathy; leukocyturia (½ of field), bacteria (many) as chronic pyelonephritis presentation.

In biochemistry analysis data significant were: hyperglycemia (7.23 mmol/l), hyper-creatinemia (94 mmol/l), low GFR (79,42 %) as confirmation of diabetes mellitus 2 type present

and its complication diabetic nephropathy. Glycemic profile 5,1 – 5,8 – 5,5 – 10,7 – 4,6 – 6,2 mmol/l. Lipid profile showed dyslipidemia with elevated concentrations of total cholesterol till 5.66 (normal ranges – < 5.2mmol/l), lipoproteids of low density till 4,05 mmol/l (N – < 3.5), lipoproteids of high density till 1,08 mmol/l (N – ≥ 0.9), index of atherogenicity was 4,24 within normal limits < 3.0. Patient didn't take any constant hypolipidemic therapy before hospitalization.

ECG during admission showed atrial fibrillation, left ventricle (LV) myocardium hypertrophy, alternation of repolarization as ST-depression in V2–V6, I, II – 1 mm.

In our patient chest X-ray was found signs of pulmonary hypertension: enlarged pulmonary arteries enlarged right atrium, elevated cardiac apex due to right ventricular hypertrophy. Enlargement of heart shadow to the left. Sclerotic changes of the aortic arch. Widening of the upper mediastinum to the right side.

Echocardiography made during hospitalization revealed: aorta: d 32,2 cm, sclerotic changes of aortic walls, dilatation of the ascending aorta, fibrosis and calcinosis of aortic valve, aortic regurgitation – I–II degree. Tricuspid valve – regurgitation I–II degree. Pulmonary trunk valve – regurgitation I stage. Pressure in pulmonary trunk is 38,7 mm Hg (n < 15). Mitral valve – cuspids are moderately thickened, fibrosis and calcinosis, regurgitation II–III degree. Ejection fraction (EF) – 54 % (N – 55–78 %). Contractility function (FC) – 28 % (N – 28–44 %). Left Ventricle: FDD – 48,9 mm (N – 35–55 mm). FSD – 35,1 mm (N – 23–38 mm). Posterior wall thickness in systole – 16,6 mm (N – 6–11mm). Intraventricular septum size in diastole– 16,2 mm (6–11 mm).

Right Ventricle: diameter – 31,9 mm (N – 9–26 mm). Wall thickness – 6,9 mm (N – 3–6 mm). Left atrium – enlarged – 44,1 mm in diameter (N – till 38 mm). Right atrium – enlarged, 48,8 mm (N – 21–37). Intraatrial septum – not changed, no defects. Conclusion: Atrial fibrillation, sclerotic changes of aorta, dilatation of the ascending aorta. Aortic regurgitation I–II degree. Mitral regurgitation II–III degree. Tricuspid regurgitation II degree. Pulmonary trunk regurgitation I stage. Moderate dilation of right and left atriums. Myocardial hypertrophy of both ventricles. Pulmonary hypertension II stage.

Abdominal ultrasound was performed also: Diffuse change of liver parenchyma with mild hepatomegaly. Congestive process in portal vein system. Cholestasis of gall bladder. Chronic non-calculous cholecystitis. Diffuse changes of pancreatic parenchyma. Kidney calcinosis. Diffuse changes of both kidneys parenchyma. Right kidney pyeloectasia and cyst.

FINAL DIAGNOSIS

Coronary artery disease: stable angina III functional class. Arterial hypertension stage 3, III degree. Permanent atrial fibrillation. CHA2DS2-VASc score 5 points. HAS-BLED Score 2 points. ATRIA Bleeding Risk Score 3 points. Chronic heart failure stage IIIC with preserved ejection fraction, III functional class by NYHA. Type 2 diabetes mellitus, complicated by diabetic nephropathy stage 2 (incipient nephropathy). Chronic Kidney Disease stage 2 (GFR – 79.42 mL/min). Chronic non calculous cholecystitis. Chronic pancreatitis. Right kidney cyst. Deforming bilateral gonarthritis and coxarthritis.

TREATMENT RECEIVED IN HOSPITAL

Clopidogrel 75 mg 1 time/day, nebivolol 5 mg 1 time/day, valsartan 80 mg 1 time/day, atorvastatin 80 mg 1 time/day, torasemide 10 mg 1 time/day, cardioarginin 5 ml IV 1 time/day for 5 days, metformine initial – 500 mg PO every 12 hr, after adjustment: 1500 mg/day.

RECOMMENDATIONS

Despite good progress in the management of patients with atrial fibrillation, it remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Reflecting the multidisciplinary input into the management of patients with AF, especially in patients with diabetes mellitus, for our patient could be recommended:

1. Diabetes is a risk factor of AF complications. Prolongation of diabetes duration in patients with AF, connected with risk of thrombo-embolism, anticoagulation therapy-related bleeding [5]. Treatment with metformin [7] seems to be associated with a decreased long-term risk of AF in diabetic patients and may even be associated with a lower long-term stroke risk [8], also for patient with established atherosclerotic cardiovascular disease therapy should begin with lifestyle

management and metformin (+ in future empagliflozin and liraglutide if needed proven to reduce major adverse cardiovascular events). Behavioral therapy designed to achieve > 5 % weight loss should be prescribed. With the body mass index (BMI) progression increases the risk for AF. Predisposing factors for obese patients may are LV diastolic dysfunction, increased sympathetic activity and inflammative changes, and abnormal atrial fatty infiltration [9]. Management of risk factors along with weight loss recommendations will be useful in reducing of AF burden and symptoms [10].

2. Mitral regurgitation (MR) as others valvular heart disease is independently associated with incident AF [10] and associated with severe LV dysfunction due to secondary MR in patients with ischemic heart disease (in our patient's case). Chronic severe secondary MR and aortic regurgitation present in our patient lead to volume overload with LV function decompensation and prognosis worsening [11].

3. In patients with heart failure with preserved ejection fraction (HFpEF) in our patient with AF it's hard to separate symptoms of HF from symptoms caused by AF appearance itself. In this case will be useful echocardiography and natriuretic peptide levels as evidence of relevant structural heart disease. The management of patients with AF and concomitant HFpEF should focus on the control of fluid balance and concomitant conditions such as hypertension and myocardial ischemia [12–13]. In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed angiotensin converting enzyme (ACE) inhibitors or angiotensin receptors blockers (ARBs) and beta blockers titrated for treatment goal of systolic BP level below than 130 mm Hg [14].

4. Uncontrolled high blood pressure induces increased risk of stroke and bleeding events and sinus rhythm conversion to AF. That's why, strict blood pressure control should be an integral part of the AF patients' management [12]. Despite the fact that ACE inhibitors or ARBs have a beneficial effect on the occurrence of overt AF, but in patients with established AF, but without LV dysfunction (our patient) or heart failure, ARBs do not prevent recurrent AF better than placebo. Further structural remodeling and sinus rhythm conversion to AF can be prevented by inhibition of the renin-angiotensin-aldosterone system [10]. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment DBP: goal of less than 130/80 mm Hg. ACE inhibitors and ARBs have the best efficacy among the drug classes on urinary albumin excretion [14].

5. The CHA2DS2-VASc score is recommended for stroke risk prediction in patients with AF by latest AF management guidelines [10]. Vitamin K antagonists (VKA) therapy are useful in AF for stroke, systemic embolism, myocardial infarction, and cardiac death prevention, effectiveness of this therapeutic strategy is higher than single or dual antiplatelet therapy with aspirin and clopidogrel (annual risk of 5.6 % for aspirin and clopidogrel vs. 3.9 % with VKA therapy). Also VKA therapy has decreased bleeding risk, comparing with dual antiplatelet therapy. That's why, antiplatelet therapy shouldn't be recommended for stroke prevention in AF patients [13].

6. Rate control is an integral part of the management of AF patients, and is often sufficient to improve AF-related symptoms. The aim of antiarrhythmic drug therapy is improvement in AF-related symptoms. Amiodarone wouldn't be a drug of choice for our patient due to increased risk of myopathy with statins and potentiating of VKAs therapy. Propafenone is contra-indicated in ischemic heart disease. Sotalol is contra-indicated in the presence of significant LV hypertrophy, systolic heart failure. Digoxin is proarrhythmic and can aggravate heart failure. Non-dihydropyridine calcium channel blockers are contra-indicated in LV failure with pulmonary congestion. Betablockers with ability to improve symptomatic and functional heart conditions through the rate control, lack of harm (from investigations published), and good tolerability in all ages [9] are useful as first-line rate control drugs in AF patients.

CONCLUSIONS

Atrial fibrillation and diabetes mellitus are very common comorbidities and with high expectance they will co-exist together in the future because of the both conditions prevalence especially in older patients group. Therefore, establishing of the most effective

and safe treatment it is very important to the subpopulation of patients with AF and DM. New studies with larger numbers of patients from different age and rage groups with diabetes and AF are needed to investigate the mechanisms of this relationship and all possible therapeutic approaches in order to determine the best possible individual management of both conditions.

REFERENCES

1. Tadic M. Type 2 diabetes mellitus and atrial fibrillation: From mechanisms to clinical practice / M. Tadic, C. Cuspidic // Archives of Cardiovascular Diseases. –2015. – Vol.108 (4). – p. 269–276.
2. Martin-Timon. Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? / Martin-Timon, C. Sevillano-Collantes, A. Segura-Galindo, F. J. Del Canizo-Gomez // World J Diabetes. – 2014. – No. 5. – p. 444–470.
3. Zhang Q. Diabetes mellitus and atrial remodeling: mechanisms and potential upstream therapies / Q. Zhang, T. Liu, C.Y. Ng, G. Li // Cardiovasc Ther. – 2014. – No. 32. – p. 233–4.
4. Chao T.F. Atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation associated with diabetes mellitus or impaired fasting glucose / T. F. Chao, K. Suenari, S. L. Chang, et al. // Am J Cardiol. – 2010. – No. 106. – p. 1615–1620.
5. Kamenov Z.A. Diabetic autonomic neuropathy / Z. A. Kamenov, L. D. Traykov // Adv Exp Med Biol. – 2012. – No. 771. – p. 176–193.
6. Otake H. Influences of autonomic nervous system on atrial arrhythmogenic substrates and the incidence of atrial fibrillation in diabetic heart / H. Otake, H. Suzuki, T. Honda, Y. Maruyama // Int Heart J.- 2009. – No. 50. - p. 627-641.
7. Chang S. H., Wu L. S., Chiou M. J., Liu J. R., Yu K. H., Kuo C. F., Wen M. S., Chen W. J., Yeh Y. H., See L. C. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. Cardiovasc Diabetol 2014; 13: 123.
8. Fatemi O., Yuriditsky E., Tsioufis C., Tsachris D., Morgan T., Basile J., Bigger T., Cushman W., Goff D., Soliman E. Z., Thomas A., Papademetriou V. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). Am J Cardiol 2014; 114: 1217–1222.
9. Overvad T. F., Rasmussen L. H., Skjoth F., Overvad K., Lip G. Y., Larsen T. B. Body mass index and adverse events in patients with incident atrial fibrillation. Am J Med 2013; 126:640.e649–617.
10. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS / Paulus Kirchhof, Stefano Benussi, Anders Ahlsson et al. //European Heart Journal. – 2016. – doi:10.1093/eurheartj/ehw210.
11. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease/ [B. Ibanez, S. James, S. Agewall, et al.] // Circulation. – 2017. – No. 1. – p. 1–57.
12. Manolis A. J. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group ‘Hypertension Arrhythmias and Thrombosis’ of the European Society of Hypertension. / A. J. Manolis, E. A. Rosei, A. Coca, et al. // J Hypertens. – 2012. – No. 30. – p. 239–252.
13. Connolly S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. / S. Connolly, J. Pogue, R. Hart, et al. // Lancet. – 2006. – No. 367. – p. 1903–1912.
14. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults / Paul K. Whelton, Robert M. Carey, Wilbert S. Aronow, et al. // JACC. – 2017. – doi : 10.1016/j.jacc.2017.11.006.

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GRANULOMATOSIS WITH POLYANGIITIS: TREAT THE PATIENT NOT SYMPTOMS

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Immunological mechanisms of appearance and therapeutic treatment strategies were discussed on example of the rare granulomatosis with polyangiitis clinical case in young patient. This vasculitis, formerly known as Wegener's granulomatosis, is a rare multisystem autoimmune disease with necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels.

KEY WORDS: granulomatosis with polyangiitis, ANCA-associated vasculitis, prognosis, sinusitis

ГРАНУЛЬОМАТОЗ ІЗ ПОЛІАНГІЇТОМ: ЛІКУЙТЕ ХВОРОГО, НЕ СИМПТОМИ

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Імунологічні механізми виникнення і терапевтичні методи лікування було обговорено на прикладі клінічного випадку рідкісного гранулематоза з поліангіітом у молодого пацієнта. Цей васкуліт, раніше відомий як гранулематоз Вегенера, являє собою рідкісне багатосистемне автоімунне захворювання з некротизуючим гранулематозним запаленням і патчі-імунним васкулітом судин малого і середнього калібру.

КЛЮЧОВІ СЛОВА: гранулематоз із поліангіітом, ANCA-ассоційованний васкуліт, прогнозування, синусит

ГРАНУЛЕМАТОЗ С ПОЛИАНГИИТОМ: ЛЕЧИТЕ ПАЦИЕНТА, НЕ СИМПТОМЫ

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Иммунологические механизмы возникновения и терапевтические методы лечения обсудили на примере клинического случая редкого гранулематоза с полиангиитом у молодого пациента. Этот васкулит, ранее известный как гранулематоз Вегенера, представляет собой редкое многосистемное аутоиммунное заболевание с некротизирующим гранулематозным воспалением и паучи-иммунным васкулитом в сосудах малого и среднего калибра.

КЛЮЧЕВЫЕ СЛОВА: гранулематоз с полиангиитом, ANCA-ассоциированный васкулит, прогноз, синусит

INTRODUCTION

Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is Anti-neutrophil Cytoplasmic Autoantibody (ANCA)-associated necrotizing vasculitis, with patho-physiological basis consisted from three components: necrotizing granulomatous inflamemation (most commonly in the upper or lower respiratory tract), granulomatous vasculitis of small and medium-sized vessels, including arteries, arterioles, capillaries and venules; and kidney disease (focal glomerulonephritis, often with necrosis and

crescent formation). The group of ANCA-associated vasculitis is a group of diseases encompassing granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg-Strauss disease (eosinophilic GPA) [1]. The earliest complaints, in over 90 % of patients with GPA, which are also the most common reasons for seeking medical attention, are usually related to upper respiratory tract problems including sinus pain, purulent nasal discharge, epistaxis, nasal ulceration, and serous otitis media. The presence of clinical signs such as supportive otitis, mastoiditis, a saddle-nose defect, and hearing loss should alert the physician for GPA [2]. Bilateral or unilateral pulmonary infiltrates are present in nearly 50 % of patients initially, with lung disease eventually developing in 85–90 % of patients [3]. Although renal involvement is clinically evident in only 11–20 % of cases at presentation, glomerulonephritis eventually develops in 77–85 % of patients, usually within the first two years of disease onset [4]. The diagnosis of GPA is difficult and often delayed due to the wide range of clinical presentations. Historically, the diagnosis of GPA has been made following the criteria of granulomatous involvement of upper and lowers respiratory tract, glomerulonephritis and varying degrees of systemic vasculitis. Fauci and colleagues [5] created effective definitive diagnostic criteria for GPA included clinical evidence of disease in at least two of three areas (upper airways, lung and kidney), and results that show disease in at least one and preferably two of these organ systems. Because biopsy based diagnosis required for GPA remains controversial, tissue diagnosis is recommended if a biopsy site is available, provided that the patient understands the risks of the procedure due to many of severe side-effects of specific for vasculitis therapy. C-ANCA directed against PR3 is most specific for GPA [6].

CLINICAL CASE

A 29-year old female was admitted 04-feb-2017 by ambulance in the emergency department of 25 Kharkiv clinical multi-field hospitals with diagnosis: Bronchial asthma attack. She complains on body temperature 38°C, ankles, hands, feet joints arthralgia, breathlessness, palpitation periodically, dyspnea and periodical cough with viscous sputum. She took at home aspirin and methylprednisolone.

ANAMNESIS MORBI

Patient was sick from august 2016, when during its trimester of pregnancy first time appeared high temperature 38°C and nasal stuffiness. Was treated by otolaryngologist with diagnosis allergic rhinitis. Medical miscarriage in 8th week. Gradually joined cough with periodical hemoptysis, pain in the throat, muso-purulent nasal discharge. Due to appearance of body temperature 38°C again and pitting edemas with pain in ankles she was consulted in Poltava regional hospital by otolaryngologist, pulmonologist and rheumatologist with conclusion: Chronic bronchitis, chronic arthritis, reactive arthritis. Patient was treated with: antibacterial, anti-inflammatory and anti-allergic drugs (exact drugs she couldn't name). Despite slight improvement she still noticed presence of periodical body temperature elevation and nasal discharge. Also in this period she noticed changes in her nose shape. In autumn 2016, she was treated 7 days in Poltava hospital with diagnosis Pneumonia.

From 22-nov-2016 until 29-nov-2016 patient was treated in Regional Kharkiv hospital with diagnosis Community-acquired bilateral pneumonia. Right sided partial spontaneous pneumothorax. Bilateral catarrhal-edematous arthritis. Chronic bilateral perceptual-cum-neurological deafness. Reactive oligoarthritis (unknown genesis), with ankle joints affection. Hypotrophy syndrome. Chronic anemia. Thrombocytosis of unknown genesis. Mitral valve prolapse I degree with regurgitation I degree. Chronic heart failure 1 stage. Was treated there with: reosorbilact, enoxaparin, pantoprazole, and glucose 5 %, dexamethasone, K+ chlorine solution, theo-phylline, fluconazole, meropenem, diclofenac and she felt better. For accurate diagnosis definition and exclusion of systemic connective tissue disorder, she was advised hospitalization to the rheumatology department but patient refused. Was recommended additional labo-ratory investigations as ANCA, anti-cardioliptin IgG, IgM; LE-cells, ANA, etc. From 05-dec-2016 she noticed relapse of symptoms (cough with bloody-purulent sputum, dyspnea at rest, numbness of low extremities, purulent discharge from ear, t – 38°C, hair and weight loss) and 12-dec-2016 she was urgently admitted in the rheumatology department of Kharkiv regional hospital and then due to heaviness of her state she was transferred to

ICU department. Chest X-ray: polysegmental pneumonia. Chest CT proved the character of pulmonary tissue changes: infiltration in S1–S2, S3–S6, and fibrosis after infiltration in S4. Several bronchoscopies were made with result: bilateral diffuse bronchitis III st., fibrinous inflammation, Streptococcus epid. 17.12.16 was made clinical sputum analysis and sputum culture: S. aureus 10^2, sensitive to cefazolin, cefepime, ceftriaxone, amoxicillin, meropenem, amikacin, ofloxacin, clindamycin. 28.12.16 it was repeated: sputum culture – Candida, sensitive to clotrimazole, nystatin. In complete blood count (CBC) were found: anemia, leukocytosis with left shift, and thrombocytosis of unknown genesis. Urine analysis revealed: leukocyturia, proteinuria, hematuria, with 24 hours proteinuria – 0,98 g/l. Also patient had hyperglycemia with glycemic profile 6,0 – 12,3 – 13,5 – 10,0 mmol/l. Ultrasound conclusion from 14.12.16: sclerotic changes of aortic and mitral valves. Mitral regurgitation II degree. Pulmonary hypertension II degree (32 mm Hg). Hepatomegaly and adipose changes of liver. Chronic cholecystitis. Chronic pyelonephritis. She was discharged after mild improvement with diagnosis: Community-acquired right-sided polysegmental pneumonia, 3 clinical group. Chronic bronchitis, exacerbation. LF I–II stage. CKD II stage: secondary nephropathy. Candydomycosis. Peripheral lymphadenopathy. Polyneuropathy of upper and low extremities, vegetal-sensual form. Reactive oligoarthritis (unknown genesis), with ankle joints affection. Hypotrophy syndrome. Metabolic cardiomyopathy. Mitral valve prolapse I degree with regurgitation II degree, pulmonary hypertension I stage. CHF 0 stage. Chronic anemia. Thrombocytosis of unknown genesis with hemorrhagic syndrome (upper and low respiratory tracts, kidneys involvement). Chronic atrophic rhino-pharyngitis. Acute left-sided purulent middle otitis, tympanum second membrane formation after acute otitis. Chronic subatrophic erosive laryngo-tracheitis. Acute bilateral catarrhal-edematous arthritis, recon-valescent. Firstly diagnosed diabetes mellitus. Hypocalcaemia. Systemic vasculitis? Blood disorder? She was treated enormous amount of drugs prescribed: gatifloxacin, vancomycin, doxycycline, piperacillin + tazobactam, cefe-pim, levofloxacin, fluconazole, nystatin, famotidine, omeprazole, etamzilat, vicasol, aspirin, vitakson, gabapentin, contrical, dexamethasone IV, methylprednisolone orally, biseptol (sulfamethoxazole, trimethoprim). During last hospitalization in Kharkiv region hospital in December 2016 several councils of physicians were made with differential diagnostics between antineutrophylic cyto-plasmic antibodies (ANCA) associated vasculitis, Goodpasture syndrome and sepsis, but these diagnoses weren't confirmed despite ANCA positive analysis (1,05 U/l (N-till 1U/l)). She was recommended: methylprednisolone 12 mg daily, moxifloxacin 400 mg daily 10 days, biseptol (sulfamethoxazole+trimethoprim) 480 mg 2 times daily, nystatin 500 mg daily 14 days, Ca supplements, consultation of hema-tologist and bone marrow trepan biopsy.

Preliminary diagnosis during hospitalization in 25 Kharkiv clinical multi-field city hospitals was Community-acquired pneumonia III clinical group, LF II stage. Anemia of unknown genesis.

ANAMNESIS VITAE

Childhood infections, injuries, tuberculosis, sexually transmitted diseases were denied by patient. Hereditary diseases are not identified. Allergic history is not burdened. Smoking - denied, not an alcohol abuser. Family history: nothing clinically significant.

OBJECTIVE EXAMINATION

Conciseness – clear, state – severe, body position – active, 37,8°C, SpO2 – 94 %. Patient can orientate himself in place, time, and her personality. Saddle shape nose deformity. Pale skin and mucosae. Thyroid: not enlarged, soft. Peripheral lymphatic nodes – not enlarged. Smoothed contours of ankle joints, with moderate functional limitations in the ankles joins. Cyanosis of the skin in the area of proximal interphalangeal hands 2, 3, 4 joints. Breath rate – 26–30 /min. Chest is symmetrical, active respiratory muscles participation in breathing, retraction of intercostal spaces. Lung percussion: dull sound in lower parts. Lung auscultation: weak breathing, whizzing, and rales in lower lung lobes. Borders of the heart: without clinically significant changes. Heart auscultation: rhythmic, heart tones – muffled, systolic soft murmur over all points of auscultation. Heart rate (HR) – 140 bts/min Pulse – rhythmic, weak, 140 bts/min. BP-120/70 mm Hg. Abdomen: normal size, symmetric, unpainful. Liver: +2 cm, moderate density, no pain during palpation in right hypochondrium. Spleen: not palpated.

Pasternatsky symptom – negative from both sides. Edemas: absent.

LABORATORY AND INSTRUMENTALTESTS

Complete blood count data presented in dynamic shows reactive or secondary thrombocytosis (RT), moderate hypochromic anemia specific for patients with systemic disorders, leukocytosis. Anti-neutrophil cytoplasmic antibodies have been known to be closely related to ANCA-associated vasculitis, including microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and single-organ ANCA-associated vasculitis, which often cause renal limited pauci-immune complex crescentic glomerulonephritis (CGN) and moderate thrombocytosis [7]. Coexistence of ANCA and the immune complex may cause a far more active immune and inflammatory state, leading to an extremely high platelet count. There have been a considerable number of articles researching the association between thrombocytosis and cytokines such as IL-6, IL-11, and thyroperoxidase in inflammatory conditions such as infection and rheumatoid arthritis. A study on Chinese people indicated that RT is not rare in ANCA-associated vasculitis patients and it has an occurrence rate of about 20 % [8]. Anemia is a common complication of patients with antineutrophil cytoplasmic antibody - associated renal vasculitis, as vessels in the kidney, skin, respiratory tract, gastrointestinal tract, and peripheral nerves are often involved [9].

Table 1

Complete blood count data in dynamic

	22.11.16	**26.11.16**	**12.12.16**	**27.12.16**	**03.01.17**	**06.02.17**	**13.02.17**	Normal Range
Hb, g/l	87	77	94	85	65	70	75	130–160
RBC, 10^{12}	4,02	3,33	3,6	3,2	2,5	2,5	2,8	4.0–5.0
Color index	0,66	0,7	0,77	0,79	0,79	0,84	0,84	0,85–1,05
WBC, 10^9	10,5	8,7	12,1	20,3	11,1	9,9	6,7	4–9
ESR, mm/h	42	42	50	40	11	31	45	1–10
Bands	8	6	6	1	2	6	1	1.06–6 %
Segments	82	74	79	73	70	72	58	47–72 %
Eosinophils	0	5	myelocytes	-	1	1	2	0.5–5 %
Monocytes	2	5	4	11	6	3	7	0.1–3 %
Lymphocytes	8	10	10	15	21	18	32	19–37 %
Platelets	781	472	1005	259	265	180	-	180–320

Although routine laboratory tests are generally nonspecific for ANCA-associated renal vasculitis, common laboratory findings in ANCA-associated renal vasculitis include leukocytosis, thrombocytosis, normochromic and normocytic anemia, and the elevation of acute-phase inflammatory proteins [9]. Anemia that occurs as a complication in these diseases is generally known as anemia of chronic disease (ACD, also called anemia of inflammation). The mechanisms of ACD are thought to be hepcidin-induced changes in iron metabolism, inadequate response of erythropoiesis, and shortening of the erythrocyte lifespan. Renal dysfunction is also an important cause of ACD. Both renal anemia and ACD are mediated through the effects of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha. Hepcidin, its increased levels seen in CKD patients, is the main regulator of iron metabolism, and its production is regulated by changes in the body's iron stores, inflammation, erythropoietic activity, and hypoxia [10].

Urinalysis of our patient showed proteinuria, leukocyturia, hematuria. 24 hours proteinuria was 0,98 g/l. Below represented urine analysis data in dynamic (see table 2.). ANCA-associated renal vasculitis is probably present in our patient according to changes in urine

analysis. Kidney biopsy wasn't performed due to heaviness of the patient's health state, but histopathological findings in some studies demonstrated that renal interstitial damage present is associated with anemia severity.

Table 2

Urine analysis data in dynamic

	22.11.16	23.12.16	03.01.17	04.02.17	07.02.17	N
ρ	1.008	1,010	1,007	1,003	1,007	1.001–1.040
glucose	–	–	–	–	–	abs
protein	0.2	1,8	1,9	0,054	0,216	abs, g/l
WBC	4–5	25–30	½ of field	10–15	½ of field	1–2
hyaline casts	–	1–2	3–4	4–5	2–3	abs
granular casts	–	–	–	5–6	1–2	abs
pH	6,0	6,0	6,0	6,0	6,0	5–7
RBC	8–10	all field	20–30	35–40	6–8	0
other	ketone bodies	menses	fungi	–	salts	

In biochemistry analysis data significant were: periodical hyperglycemia (7.4–6,1 mmol/l), elevation of creatinine levels (124–138 mmol/l), high level of potassium (5,62 mmol/l within normal limits 3,5–5,1 mmol/l), elevation of seromucoids concentrations – 721 U (N – 135–200) and CRP – 60 mg/l (N 0–5). Hyperglycemia was a nearly universal occurrence in this severely ill population of medical patients. The severity and frequency of hyperglycemia during critical illness is determined in part by acute stimuli, including corticosteroids, exogenous catecholamine, and carbohydrates. Even among patients with normal baseline glucose control, higher (but still normal) glycated hemoglobin level was associated with more frequent and severe hyperglycemia. During critical illness, the usual correlation between HbA1c and plasma glucose is shifted, presumably through loss of homeostatic reserve [11]. Among immunological and serological investigations remarkable and clinically significant, diagnosis proven were: ANCA titer – 1,05 U/l (N till 1,0), levels of rheumatoid factor – 120 mU/l (N-negat) which are specific for ANCA-associated vasculitis formerly known as Wegener's vasculitis. Rheumatoid factor is positive in a low titer in two thirds of patients, whereas antinuclear antibody is present in 10–20 % of patients [6]. Also were made: anticardiolipin IgM – 1,11 U/l (N till 7 U/l), ANA – negat., LE-cells – negat., ACCP – negat., IgG to herpes – negat., IgG to CMV – negat., IgM to phospholipid and glycoprotein – negat, HIV – negat., VCA IgM and VCA IgG – negat., PCR for herpes, cytomegalovirus (CMV), Epstein-Barr virus (VCA) – negat., Wassermann's reaction (RW) – 13.02.17 No. 9284-negat. Blood culture repeated several times 12.12; 21.12; 22.12; 23/12/16 showed no grows, but in sputum was found sputum S. pneumonias 10^8, sensitive to ceftriaxone. ECG during admission showed sinus rhythm, sinus tachycardia with HR – 150 beats in min., metabolic disturbances.

In our patient chest X-ray during admission in a direct and the right lateral projection was found on an inspiration and an exhalation is defined emphysema, diffuse pneumosclerosis. On the right, in the lower lobe, there is a focus of the lung tissue low transparency due to infiltration without clear contours. In the basal zones on both sides, there is an increase in pulmonary pattern according to the strend type. Sinuses are free. Ordinary diaphragm, normal excursion. Cardiovascular shadow within normal limits. Conclusion: Pneumosclerosis. Right-sided pneumonia.

Spirometry from 14.02.17. – VLC – 2,99l (84,3 % from normal), FEV1, l – 1,67 (54 % from normal), FEV1/FVC – 99,7 (0,9). Conclusion: stenosis of intrathoracic respiratory ways.

Otolaryngologist conclusion was: chronic rhino-pharyngitis, chronic left-sided cochlea-neuritis. Neuropathologist: polyneuropathy of upper and low extremities, vegetal-sensual form. Pulmonologist considered that taking into consideration patient's clinical examination and laboratory investigations data, diagnosis of primary ANCA – associated systemic vasculitis (it is necessary to make differential diagnosis

between Goodpasture's syndrome and Wegener's granulomatosis) could be the most reliable in this case.

After treatment in the therapy department was repeated chest x-ray to check effectiveness of therapeutic strategy chosen. On the control chest X-ray positive dynamics seen. Infiltration is not present. There is some increase of the pulmonary pattern in the medial parts, because of the vascular component. Structural roots. Diaphragm is normal. Sinuses are free. Enlargement of heart shadow as the left border of the heart is widened. Conclusion: the residual changes after pneumonia.

FINAL DIAGNOSIS

Granulomatosis with polyangiitis with involvement of upper and lower respiratory ways, kidneys. Chronic rhino-pharyngitis. Chronic left-sided cochlea-neuritis. Polyneuropathy of upper and low extremities, vegetal-sensual form. Metabolic cardiomyopathy. Mitral valve prolapse I degree with regurgitation II degree, pulmonary hypertension I stage. CHF 0 stage. Anemia of chronic disease, moderate.

TREATMENT RECEIVED IN HOSPITAL

Levofloxacin 500 mg 1 time\day, ceftriaxone 2 g IM 1 time/day, inhalations with moistened O2, dexamethasone 8mg IV 1 time daily, Hartmann's solution IV 200,0 ml, ivabradin 5 mg 2 time\day, acetylcysteine 400 mg a day, berodual (ipratropium bromide+fenoterol) inhalation 2 times/day; a combination of methylprednisolone in dosage 64 mg/day and methotrexate in dosage 20 mg/day as vasculitis-specific treatment.

RECOMMENDATIONS

Generally the prognosis of GPA has dramatically improved with the introduction of immunotherapy, there is still significant morbidity from the disease itself (86 %) or side effects from the therapy (42 %) [1]. The majority of patients, despite intensive treatment, experience relapses during treatment or even in remission. As disease's relapse is associated with poorer prognosis and increased mortality, effective treatment and prevention of further relapses in strictly recommended. Based on these therapeutic goals for our patient could be recommended:

1. The mainstay of treatment for granulomatosis with polyangiitis (GPA) is a combination of corticosteroids and cytotoxic agents. The choice of methotrexate with glucocorticoids combination as initial therapy was based on absence in our patient case non-organ-threatening and non-life-threatening disease (no evidence for «active» glomerulonephritis or no organ-threatening or life-threatening manifestations, patients may have rhinosinusitis, arthritis, and/or pulmonary nodules). For our patient was prescribed a combination of methylprednisolone in dosage 64 mg/day and methotrexate in dosage 20 mg/day for 1 month with adjustment of therapy in future.

2. From November 2016 patient has hyperglycemia, so was recommended glycemic levels control in future with investigations for hyperglycemia genesis definition (C-peptide, HbAc1 etc.).

3. Patients with GPA should have regularly scheduled follow-up visits with the physician primarily responsible for managing his or her disease. Since recurrences occur frequently, patients should be monitored closely clinically, with radiologic studies and laboratory examinations that include renal function, erythrocyte sedimentation rate (ESR), ANCA levels, and urinalysis.

4. Prophylaxis against Pneumocystis pneumonia is essential while patients are receiving conventional therapy for GPA. This can be achieved with trimethoprim-sulfamethoxazole single-strength once daily or double-strength formulation three times per week. Dapsone 100mg daily can be used in sulfa-allergic patients. Also baseline bone mineral density should be evaluated because of high risk for glucocorticoid-induced osteoporosis. Routine laboratory tests are nonspecific in granulomatosis with polyangiitis. Rheumatoid factor is positive in a low titer in two thirds of patients, whereas antinuclear antibody is present in 10–20 % of patients. Whether tissue diagnosis is always required for GPA remains controversial. As the therapy for severe GPA is not benign, tissue diagnosis is recommended if a biopsy site is available, provided that the patient understands the risks of the procedure. C-ANCA directed against PR3 is most specific for GPA.

5. Causes of anemia in our patient with ANCA-associated renal vasculitis are multifactorial, and that while renal anemia is easily missed, it is the most frequent and influential cause of anemia in patients with

ANCA-associated renal vasculitis. There is a possibility that the treatment for anemia itself would lead to an improvement in the prognosis of patients with ANCA-associated renal vasculitis [4]. In the future, therefore, it will be important to investigate the efficacy of earlier treatment initiation for anemia, the optimal timing of anemia intervention and the effectiveness of erythropoietin therapy.

CONCLUSIONS

Autoimmune diseases affect 5 to 7 % of people, are commoner in women of childbearing age, and are frequently encountered in pregnancy. They may remit or improve during pregnancy, but can flare or present in pregnancy with disastrous consequences. Otorhinolaryngologist is the first physician to contact for the majority of patients with GPA. This diagnosis must always be taken into consideration in patients with recurrent upper respiratory tract infections, otitis, mucosal ulcers and laryngitis. Proper and early diagnosis is crucial for imminent therapy implementation and allows avoiding irreversible organ damage.

REFERENCES

1. Harper L. ANCA-associated renal vasculitis at the end of the twentieth century-a disease of older patients. / Harper L., Savage C. O. // Rheumatology (Oxford). – 2005. –No. 4. – p. 495–501.
2. Kubaisi B. Granulomatosis with polyangiitis (Wegener's disease): An updated review of ocular disease manifestations / B. Kubaisi, K. A. Samra, C. S. Foster // Intractable Rare Dis Res. – 2016. – No. 5(2). – p. 61–69.
3. Cordier J. F. Pulmonary Wegener's granulomatosis. A clinical and imaging study of 77 cases. / J. F. Cordier, D. Valeyre, L. Guillevin, R. Loire, J. M. Brechot // Chest. -1990. – No. 97. – p. 906–912.
4. Hoffman G. S. Wegener granulomatosis: an analysis of 158 patients. / G. S. Hoffman, G. S. Kerr, R. Y. Leavitt, [et al.] // Ann Intern Med. – 1992. – No. 116(6). – p. 488–98.
5. Fauci A.S. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. / A. S. Fauci, B. F. Haynes, P. Katz, S. M. Wolff // Ann Intern Med. -1983. – No. 98(1). – p. 76–85.
6. Bossuyt X. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. / X. Bossuyt, C. Tervaert, Y. Arimura, [et al.] // Nat Rev Rheumatol. – 2017. – No. 13(11). – p. 683–692.
7. Jennette J. C. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. / J. C. Jennette, R. J. Falk, P. A. Bacon, [et al.] // Arthritis Rheum. – 2013. – No. 65(1). – p. 1–11.
8. Wang Y. The clinical and pathological characteristics of Chinese elderly patients with anti-neutrophil cytoplasmic autoantibodies associated small vessel vasculitis. / Y. Wang, M. H. Zhao, J. Yu, et al. // Exp Gerontol. – 2004. – No. 39(9). – p. 1401–5.
9. Tetsuya K. Anaemia is an essential complication of ANCA-associated renal vasculitis: a single center cohort study / K. Tetsuya, J. Usui, S. Kaneko, et al. // BMC Nephrol. - 2017. – No. 18. – p. 337–345.
10. Weiss G. Anemia of chronic disease. / G. Weiss, L. T. Goodnough // N Engl J Med. – 2005. – No. 352(10). – p. 1011–1023.
11. Cely C. M. Relationship of Baseline Glucose Homeostasis to Hyperglycemia During Medical Critical Illness / C. M. Cely, P. Arora, A. A. Quartin [et al.] // Chest. – 2004. – No. 126(3). – 879–887.

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VENTRICULAR MURAL THROMBUS IN PATIENT WITH LEFT VENTRICULAR ANEURYSM AFTER MYOCARDIAL INFARCTION

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On the example of the clinical case of newly diagnosed mural thrombus in patient with post ST-elevation myocardial infarction chronic aneurysm formation, probable risk of further tromboembolism and anticoagulation benefit was discussed. Recommendations on lifestyle modification and medicament treatment tactics are described for prevention of new mural thrombi formation.

KEY WORDS: STEMI, mural thrombus, anticoagulation, risk, ventricular aneurism

ПРИСТІНКОВИЙ ТРОМБ У ПАЦІЄНТА ІЗ АНЕВРИЗМОЮ ЛІВОГО ШЛУНОЧКА ПІСЛЯ ПЕРЕНЕСЕНОГО ІНФАРКТУ МІОКАРДА З ЕЛЕВАЦІЄЮ ST-СЕГМЕНТУ

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На прикладі клінічного випадку вперше діагностованого пристінкового тромбу у пацієнта з аневризмою лівого шлуночка після перенесеного інфаркту міокарда з елевацією ST-сегменту обговорили можливий ризик подальших тромбоемболічних ускладнень і переваги антикоагулянтної терапії. Описано рекомендації з модифікації способу життя і тактики лікування для запобігання утворення нових пристінкових тромбів.

КЛЮЧОВІ СЛОВА: STEMI, пристінковий тромб, антикоагулянтна терапія, ризик, шлуночкова

ПРИСТЕНОЧНЫЙ ТРОМБ У ПАЦИЕНТА С АНЕВРИЗМОЙ ЛЕВОГО ЖЕЛУДОЧКА ПОСЛЕ ПЕРЕНЕСЕННОГО ИНФАРКТА МИОКАРДА С ЭЛЕВАЦИЕЙ ST-СЕГМЕНТА

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На примере клинического случая впервые диагностированного пристеночного тромба у пациента с развившейся постинфарктной аневризмой после перенесенного инфаркта миокарда с ST- элевацией обсудили вероятный риск дальнейших тромбоэмболических осложнений и преимуществ антикоагулянтной терапии. Описаны рекомендации по модификации образа жизни и тактике лечения для предотвращения образования новых пристеночных тромбов.

КЛЮЧЕВЫЕ СЛОВА: STEMI, пристеночный тромб, антикоагулнтная терапия, риск, аневризма желудочка

INTRODUCTION

Left ventricular (LV) thrombus formation is a frequent complication in patients with acute anterior myocardial infarction (MI), occurring in at least 5 % of patients. Left ventricular thrombus is associated with increased risk of embolism. [1]. In the context of STEMI, prolonged ischemia results in subendocardial and endothelial injury and increased concentration of procoagulant factors, whereas akinetic areas of necrotic myocardium lead to blood stasis, especially at the LV apex [2]. Two-dimensional transthoracic echocardiography is the most effective diagnostic technique in this setting and can be quickly performed at the bedside but can lead to misdiagnoses due to difficult echo windows,

artifact, or the misinterpretation of LV trabeculations or chordae. [3]. In a recent article by Wada et al [4] was demonstrated the excellent diagnostic power of echo contrast for the diagnosis of LV thrombus in 392 patients with anterior MI. Echo contrast had 100 % sensitivity and specificity compared with left ventriculography and/or multidetector computed tomography used as gold standard [5]. Anticoagulation therapy reduces both risks of thrombus formation and subsequent embolization, but leads to increased risk of bleeding. [6] Therefore, accurate detection and exclusion of LV thrombus in patients with coronary artery disease (CAD) are very important [7]. In observational studies and meta-analyses, anticoagulant therapy is recommended in order to minimize embolization risk. An oral vitamin K antagonist, warfarin, has been being used as an anticoagulant for this purpose for a long period of time. New oral anticoagulants (dabigatran, rivaroxaban, apixaban, etc.) were found to be non-inferior or superior compared to warfarin in prevention of thromboembolism in patients with nonvalvular atrial fibrillation [8].

CLINICAL CASE

A 72-year old man was admitted by ambulance in the emergency department of 25 Kharkiv city clinical multi-field hospital with complains on anxiety, general weakness, trembling inside, palpitation periodically, dyspnea and chest pain after mild physical activity.

ANAMNESIS MORBI

Diagnosis of arterial hypertension (AH) and coronary artery disease were established 20 years ago (in 1993 patient had acute anterior-lateral myocardial infarction). Usual blood pressure levels by patient's words are 170/90–100, he receives constant therapy with angiotensin-converting enzyme inhibitors (ACEIb). Also patients receive constant therapy with aspirin 75 mg/day around 5 years long**.** This time he felt worse 3 days before hospitalization, when appeared palpitation, trembling inside and anxiety, increased general weakness. Was administered by ambulance in cardiology department of 25 city hospital.

ANAMNESIS VITAE

Childhood infections, injuries, tuberculosis, sexually transmitted diseases were denied by patient. Hereditary diseases are not identified. Allergic history is burdened (penicillin). Smoking - denied, not an alcohol abuser.

OBJECTIVE EXAMINATION

Conciseness - clear, state – moderate severe, body position – active. Patient can orientate himself in place, time, his personality. Pale skin and mucosae. Thyroid: not enlarged, soft. Musculoskeletal system – no changes. Breathe rate – 16–18 /min. Lung percussion: no clinically significant changes. Lung auscultation: hard breathing. Borders of the heart: left border – outside of midclavicular left line on 2 cm. Heart auscultation: arrhythmic, extrasystoles 2–3 in min, heart tones – muffled, diastolic soft murmur over apex. Pulse – arrhythmic, 76 bts/min. Blood pressure 145/80 mm Hg. Abdomen: normal size, symmetric, unpainful. Liver: normal size, no pain during palpation in right hypochondrium. Spleen: normal. Pasternatsky symptom – negative from both sides. Edemas: absent. In admitting office, preliminary diagnosis was: Coronary Arteries Disease: post-MI (1993) atherosclerotic cardiosclerosis. Arterial hypertension III stage, III degree, very high risk. Ventricular extrasystolic arrhythmia. Chronic Heart Failure IIA stage, III functional class by NYHA.

LABORATORY AND INSTRUMENTAL TESTS

Complete blood count data from 09-oct-2017: no clinically important changes, all other parameters within normal limits. Urinalysis: all parameters within normal limits. In biochemistry analysis data significant were: abnormal level ALS 0,80 (0,1–0,445 mkmol/h*ml) and AST 0,98 (0,1–0,68 mkmol/h*ml). Lipid profile showed dyslipidemia with elevated concentrations of total cholesterol till 6.03 (normal ranges – < 5.2 mmol/l), lipoproteins of low density till 4,19 mmol/l (N – < 3.5), lipoproteins of high density till 1,49 mmol/l (N – < 0.9), index of atherogenicity was 3,37 within normal limits < 3.0. Patient didn't take any constant hypolipidemic therapy before hospitalization. ECG during admit ion showed sinus rhythm, HR 98 bts, ventricular extrasystolic arrhythmia, classical for chronic aneurism ST-elevation without dynamics in antero-lateral leads V2–V5 leads with T-wave inversion. In our patient chest X-ray was found enlargement of heart

shadow to the left, aorta with sclerotic changes and no mediastinum enlargement seen. Echocardiography was also made: Aorta: dilated, capsids are thickened. Ascending aorta – d 38 (20–37 mm). Aortic regurgitation I degree. Tricuspid valve – no regurgitation. Pulmonary trunk valve – no regurgitation. Pressure in pulmonary trunk is 19,0 mm Hg (< 15). Mitral valve – capsids are moderately thickened, movements of leaflets is in different direction, anterior capsid in left atrium cavity during systole, regurgitation II degree. Ejection fraction (EF) – 36 % (N – 55 – 78 %). Function of contractility – 41 % (N – 28–44 %). Left Ventricle: FDD – 53 mm (N – 35–55 mm), FSD – 42 mm (N – 23–38 mm), posterior wall thickness in systole– 12,2 mm (N – 6– 3 mm). Intraventricular septum size in diastole– 6,0 mm (6–11 mm). Additional chorda in LV cavity. In LV cavity situated round shape parietal thrombus 27*29 mm. Right Ventricle: diameter – 28,1 mm (N – 9–26 mm), wall thickness – 6,0 mm (N – 3–6 mm). Left atrium – enlarged – 44,1 mm in diameter (N – till 38 mm). Right atrium – not enlarged, 36 mm (N – 25–37). Interatrial septum – not changed, no defects. Conclusion: Sclerotic changes of aorta. Aortic regurgitation I degree. Mitral regurgitation II degree. Akinesia of LV apical segments and intraventricular septum with diastolic dysfunction of LV. Moderate dilation of left atrium. Chronic heart aneurism of LV with mural thrombus.

Abdominal ultrasound performed: Liver: Right lobe – 131 (N-till 150 mm), left lobe thickness – 64 (N-till 65 mm), moderate echogenicity, structure is homogenous. Ductular system is not changed. Gall bladder: 43*19 mm. Wall thickness is increased, normal shape. Pancreas: head – 27 mm (N – 24–30 mm), tail – 26 mm (N – 17–28), body – 24 mm (N – 12–17). Increased parenchyma echogenicity, homogenous. Ductular system is not changed. Spleen: 76*27 cm. Normal echogenicity, structure is homogenous. Right kidney: 90*45 mm, parenchyma – 17 mm, moderate echogenicity, structure is homogenous, not changed, microlithiasis. Left kidney: 91*49 mm, V = 84 cm/c, parenchyma – 16 mm, normal echogenicity, structure is homogenous, enlarged due to pelvis dilation. Conclusion: Diffuse changes and fibrosis of pancreas parenchyma. Calculous kidney disease. Left sided pyeloectasia.

FINAL DIAGNOSIS

Coronary Artery Disease: stable angina III functional class, postinfarction cardiosclerosis (1993). Chronic heart aneurism with mural thrombus. Mitral regurgitation II degree, aortic regurgitation I degree. Arterial Hypertension III degree, III stage, very high risk. Ventricular extrasystolic arrhythmia. HAS-BLED Score – 3 points. Chronic Heart Failure IIIC stage with left ventricle systolic dysfunction (EF – 36 %), III functional class by NYHA. Chronic pancreatitis. Chronic pyelonephritis, microlithiasis.

TREATMENT RECEIVED IN HOSPITAL

Perindopril 4 mg 1 time\day from admission, nebivolol 2,5 mg 1 time/day from admission, rosurvastatin 10 mg 1 time a day from admission, aspirin 100 mg 1 time daily from admission, fondaparinux 2,5 mg sub-cutaneously from admission, tiotriazolin (metabolic) 4,0 ml IV 1 time\day from admission.

RECOMMENDATIONS

Summarizing data from 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [9] and 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [10], the following may be applicable for our patient after discharge from hospital and for prevention of further mural thrombi formation and thromboembolic episodes appearance:

1. For mural thrombi, once diagnosed, oral anticoagulant therapy should be considered for up to 6 months, guided by repeated echocardiography and with consideration of bleeding risk and need for concomitant antiplatelet therapy [11].

2. Secondary mitral valve regurgitation: LV remodeling with lateral and apical displacement of the papillary muscles, leaflet tethering, and annular dilatation are a common cause of secondary (functional) mitral regurgitation. While transthoracic echocardiography is fundamental for the initial diagnosis, transesophageal echocardiography may be needed for better definition of the mechanism and severity of mitral regurgitation. The severity of mitral regurgitation may improve with reperfusion and aggressive medical treatment, including diuretics and arterial

vasodilators. In our patients case can be treated symptomatically without surgical correction needed [9].

3. ACE-blockers is recommended and should be up-titrated to the maximum tolerated dose, in addition to a beta-blocker, for symptomatic patients with CHF with reduced ejection fraction (HFrEF) to reduce the risk of HF hospitalization and death. A beta-blocker is recommended initially at a low dose with gradually up-titration to the maximum tolerated dose, in addition an ACE-Id or ARB if ACEIb is not tolerated or contraindicated, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death. Beta-blockers are also effective agents for angina control in our patient's case [10].

4. Mineralocorticoid/aldosterone receptor antagonists are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF $\leq$ 35 %. Can be avoided in our patient case as EF is 36 %, but used as AH treatment as needed [9, 11].

CONCLUSIONS

Left ventricular thrombus is an important complication of acute myocardial infarction that impacts embolic event risk and anticoagulant therapy. Improved understanding of post-MI thrombus in the current era is critical for optimization of diagnostic testing strategies. Advances in MI management, including prompt and effective coronary reperfusion, have yielded improvements in LV function and remodeling. Widespread use of antiplatelet agents may potentiate the benefits of reperfusion, thereby lessening the likelihood of LV thrombus.

REFERENCES

1. Okuyan E. Risk factors for development of left ventricular thrombus after first acute anterior myocardial infarction-association with anticardiolipin antibodies / [E. Okuyan, B. Okcun, et al.] // Thrombosis Journal. – 2010. – No. 8. – p. 8–15.
2. Delewi R. Left ventricular thrombus formation after acute myocardial infarction. / R. Delewi, F. Zijlstra, J. J. Piek // Heart. – 2012. – No. 98. – p. 1743–1749.
3. Gianstefani S. Incidence and Predictors of Early Left Ventricular Thrombus After ST-Elevation Myocardial Infarction in the Contemporary Era of Primary Percutaneous Coronary Intervention / [S. Gianstefani, A. Douiri, et al.] // http://dx.doi.org/10.1016/j.amjcard.2013.12.015
4. Wada H. Contrast echocardiography for the diagnosis of left ventricular thrombus in anterior myocardial infarction. / [H. Wada, T. Yasu, K. Sakakura, et al.] // Heart Vessels. – 2013, [e-pub ahead of print].
5. Kurt M. Impact of contrast echocardiography on evaluation of ventricular function and clinical management in a large prospective cohort. / [M. Kurt, K. A. Shaikh, L. Peterson, et al.] // J Am Coll Cardiol. – 2009. – No. 53. – p. 802–810.
6. Kontny F. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. / [F. Kontny, J. Dale, U. Abildgaard, et al.] // J Am Coll Cardiol. – 1997. –No. 30. – p. 962–969.
7. Monvadi B. S. Clinical, imaging, and pathological characteristics of left ventricular thrombus: A comparison of contrast-enhanced magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography with surgical or pathological validation. / [B. S. Monvadi, J. Chelif, et al.]. // American Heart Journal. – 2006. – No. 151 (1). – p. 75–84.
8. Yildirim E. Successful resolution of left ventricular thrombus with apixaban treatment. / [E. Yildirim, K. Kalkan, E. Ipek, et al.]. // International Journal of the Cardiovascular Academy. – 2016. – No. 2. – p. 57–58.
9. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation / [B. Ibanez, S. James, S. Agewall, et al.] // European Heart Journal. – 2017. – p. 1–66.
10. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure / [P. Ponikowski, A. Adriaan, et all.] // European Heart Journal. – 2016. – p. 1–85.
11. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation - Web Addenda / [B. Ibanez, S. James, S. Agewall, et al.] // European Heart Journal. – 2017. – p. 1–8.

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FAILED PREHOSPITAL FIBRINOLYSIS IN PATIENT WITH PERCUTANEOUS CORONARY INTERVENTION IN ST-ELEVATION MYOCARDIAL INFARCTION

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On the example of the clinical case of newly diagnosed ST-elevation myocardial infarction combination of different reperfution strategies and their benefit was discussed. Recommendations on lifestyle modification and medicament treatment tactics are described.

KEY WORDS: STEMI, thrombolysis, effective treatment, coronarography

НЕЕФЕКТИВНИЙ ДОГОСПІТАЛЬНИЙ ФІБРИНОЛІЗИС У ПАЦИЄНТА З ЧРЕЗШКІРНОЮ КОРОНАРНОЮ ІНТЕРВЕНЦІЄЮ У ВИПАДКУ ІНФАРКТУ МІОКАРДА З ЕЛЕВАЦІЄЮ ST-СЕГМЕНТУ

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На прикладі клінічного випадку вперше виявленого інфаркту міокарда з елевацією ST-сегменту було розглянуто комбіновану реперфузію за допомогою різних методик і обговорено її переваги. Описано рекомендації з модифікації способу життя, а також тактику медикаментозного лікування.

КЛЮЧОВІ СЛОВА: STEMI, тромболізис, ефективне лікування, коронарографія

НЕЭФФЕКТИВНЫЙ ДОГОСПИТАЛЬНЫЙ ФИБРИНОЛИЗИС У ПАЦИЕНТА С ЧРЕЗКОЖНОЙ КОРОНАРНОЙ ИНТЕРВЕНЦИЕЙ В СЛУЧАЕ ИНФАРКТА МИОКАРДА С ЭЛЕВАЦИЕЙ ST-СЕГМЕНТА

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На примере клинического случая впервые выявленного инфаркта миокарда с элевацией ST-сегмента была рассмотрена комбинированная реперфузия с помощью различных методик и обсуждены ее преимущества. Описаны рекомендации по модификации образа жизни, а также тактика медикаментозного лечения.

КЛЮЧЕВЫЕ СЛОВА: STEMI, тромболизис, эффективное лечение, коронарография

INTRODUCTION

Ischaemic heart disease accounts for almost 1.8 million annual deaths in the world and around 20 % of all deaths in Europe, the ST-elevation myocardial infarction (STEMI) incidence rate ranged from 43 to 144 per 100 000 per year in different European countries [1]. Primary percutaneous coronary intervention (PPCI) is preferred for most patients if it can be performed with less than a 90 minute delay from the point of first medical contact. However, fibrinolysis (FL) remains an important therapeutic modality, due to limited availability of PPCI. Primary failure of fibrinolysis manifested clinically as persistent or worsening chest pain or/and ST segment elevation, hemodynamic instability or heart failure [2]. Meta-analysis of randomized controlled trials maden by Vincent Roule et others [3] showed that compared with PPCI, prehospital fibrinolysis in the early period

associated with better prognosis, included similar mortality rates, lower rates of cardiogenic shock, and higher rates of stroke in patients with ST-segment elevation myocardial infarction (STEMI). Despite the fact that the number of studies compared were relatively low, results supported an hypotise that prehospital FL with transfer to percutaneous coronary intervention (PCI) centers is a valid alternative to PPCI, which allows potential limitation of resources allocated to developing proximity 24/7 PCI facilities [4]. The benefit of PPCI over prehospital FL is not clear among patients managed early in the prehospital setting, but both of them are time-dependent with similar rates of mortality [3].

CLINICAL CASE

A 62-year old man was admitted by ambulance in the emergency department (ED) of Kharkiv Railway Clinical Hospital No. 1 with complains on periodical pressing pain in the heart without irradiation, general weakness, discomfort in the chest.

ANAMNESIS MORBI

06-sept-2017 in 3p.m. after intensive physical exertion he felt extremely bad, appeared intense pressing pain behind sternum with irradiation to the right hand, nitroglycerin tablet sublingual didn't help, ambulance made ECG and patient was delivered to local hospital with diagnosis STEMI, where was done thrombolysis with recombinant plasmin activator tenecteplase, prescribed morphine, nitroglycerin and heparin. As there is no possibility to transfer patient in appropriate timelines from Krasnograd to Kharkiv for primary percutaneous coronary intervention, was decided to make fibrinolysis with further PCI if needed. After slight improvement of patient state, patient was referred for specific treatment in the cardiological department of Kharkiv Railway Clinical Hospital No. 1. From 2007 – he has history of Arterial Hypertension (AH) with blood pressure (BP) levels 170-190/100 mm Hg, patient took medications only from time to time. According to patients statement, in the summer 2017 he had transient ischemic attack (TIA) (with symptoms as numbness of the right arm, rigidity of the mouth right angle), which resolved itself without any treatment. Patient has cardio-vascular risk factors in family history: mother of patient had stroke.

ANAMNESIS VITAE

Childhood infections, injuries, sexually transmitted diseases were denied by patient. Bone tuberculosis in the childhood with necroectomy and hip joint defect plastic. Hereditary diseases are not identified. Allergic history is not burdened. Smoking – denied, not alcohol abuser.

OBJECTIVE EXAMINATION

Conciseness – clear, state – severe, body position – active. Patient is orientated in place, time, his personality. Pale skin and mucosae, lips cyanosis. Thyroid: no pathological changes. Musculoskeletal system – left hip shortened after operation on around 10 cm. Breath rate – 22–24 /min. Lung percussion: no clinically significant changes. Lung auscultation: vesicular breathing. Borders of the heart: left border – outside of midclavicular left line on 1.5 cm, others – within normal parameters. Heart auscultation: rhythmic, heart tones – muffled. Pulse – rhythmic, 90 bts/min. BP 150/80 mm Hg. Abdomen: normal size, symmetric, unpainful. Liver: liver margin near the rib cage, soft, no pain during palpation in right hypochondria. Spleen: normal. Pasternatsky symptom – negative from both sides. Edemas: not present.

In ED, preliminary diagnosis was: Coronary Arteries Disease: circular STEMI (06-oct-2017). Trombolysis with tenecteplase. Arterial hypertension III stage, II degree, very high risk. Heart failure by Killip I stage.

LABORATORY AND INSTRUMENTAL TESTS

Complete Blood Count from 06-oct-2017: elevation of platelets 348 * 10^9/l (N 180–320), all other parameters within normal limits.

Urinalysis: all parameters within normal limits.

In biochemistry analysis data significant were: abnormal level of Troponin I – 1,92 mkg/l (N < 0,01), constant elevation of CFK-MB and CFK-NAC concentrations from admition time till coronarography / PCI (6-oct - 2017 at 7p.m. – 13,8 u/l, 7-oct-2017 at 7a.m. – 64,6 u/l, at 1p.m. – 70,9 u/l respectively).

ECG during admition showed classical STEMI ECG changes as pathological ST segment elevation in II, III, V1-V6 leads with T-wave inversion in lead, presence of Q wave > 3 mm only in aVR, IIId leads, ST –

depression in aVL, sinus rhythm, heart rate – 88 bts/min, which was the confirmation of failed pre-hospital fibrinolysis.

In our patient Chest X-ray data was enlargement of heart shadow to the left, aorta without specific changes but enlarged mediastinum seen.

Because of elevation of serum cardiac enzymes levels, progression of ECG STEMI picture and presence of pain syndrome despite FL, coronary angiography was performed: Left type of coronary blood circulation. Diffuse atherosclerotic changes of vascular system. Left coronary artery: truncus – no specific changes, anterior descendant artery – stenosis 60 % in proximal segment, tandem stenosis 80 % in the middle segment, subocclusion in distal segment, intermedial artery – 80 % stenosis, left circumflex artery – 70 % stenosis (atherosclerotic plaque with instability signs). Right coronary artery: hypoplastic, area with atherosclerotic narrowing and occlusion 100 % before marginal brach (TIMI-0 – no antegrade flow beyond the point of occlusion).

For the occlusion in right coronary artery was done PCI with stent «Integriti (BMS)» 2,5*26 mm. Blood flow after stenting TIMI-3 (normal flow with complete filling of the distal territory).

Echocardiography after coronary angiography was maden: aorta with sclerotic wall changes, d – 33,9 (N – 20–37). Ascending aorta – d – 39,3 (20–37 mm). Aortic regurgitation II stage. Tricuspid valve – regurgitation I stage. Pulmonary trunk valve – N. Pressure in pulmonary trunk is 21,7 mm Hg (< 15). Mitral valve – regurgitation I stage. EF – 52 % (N – 55–78 %). FS – 27 % (N – 28–44 %). Hypokinesia of apex segment, upper part of intraventricular septum and posterior-diaphragmal wall of LV myocardium.

Left Ventricle: FDD – 48,5 mm (N – 35–55 mm), FSD – 35,6 mm (N – 23–38 mm), posterior wall thickness – 14,9 mm (N – 6–13 mm). Intraventricular septum size – 14,4 mm (6–11 mm) – enlarged.

Right Ventricle: Diameter – 25,2 mm (N – 9–20 mm), wall thickness – 6,0 mm (N – 3–6 mm). Left atrium – not enlarged – 33,5 mm in diameter (N – till 38 mm). Right atrium – not enlarged – 35,6 mm in diameter (N – 25–37). Interatrial septum – not changed. Valvular apparatus is not changed, except tricuspid valve – regurgitation I degree. Conclusion: Aortic atherosclerosis, valvular system of aortic and mitral valves. Dilation of ascending part of aorta, aortic regurgitation II stage. Hypertrophy of the left ventricle myocardium by concentric type. Hypokinesia of apex segment, upper part of intraventricular septum and posterior-diaphragmal wall of LV myocardium. Decreased pump function and increased diastolic rigidity of left ventricle myocardium. Pulmonary hypertension I degree.

In 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, reperfusion therapy is recommended for all patients with symptoms of ischemia of ≤ 12 hours duration and persistent ST-elevation. In this case patients should be transferred to a PCI-capable facility as soon as possible after bolus of lytics administration [1]. For patients presenting in a non-PCI centre, door-in to door-out time, defined as the duration between arrival of the patient at the hospital to discharge of the patient in an ambulance en route to the PCI centre, is a new clinical performance measure, and ≤ 30 min is recommended to expedite reperfusion care [5]. In cases similar to our patient case when initial fibrinolytic treatment is failed (ST-segment resolution < 50 % within 60–90 min of fibrinolytic administration) with manifestation as chest pain, further elevation serum concentrations of main cardiac biomarkers should be performed an emergent PCI [1]. The key issue is the optimal time delay between successful lysis and PCI. Different strategies were observed: from a median of 1.3 h in the Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction (CAPITAL AMI) trial to 17 h in the Grupo de Analisis de la Cardiopatıa Isque´mica Aguda (GRACIA)-1234 and STREAM trials [6]. Based on this analysis, in case of successful fibrinolysis routine coronary angiography PCI was recommended to perform in timelines from 2 to 24 hours, as it was done in our clinic.

After coronarography and PCI with stent application ECG showed sinus rhythm, negative T-waves in III, aVL, V1; heart rate – 85 bts/min.

Holter 24-monitoring performed after PCI showed: sinus rhythm with HR variability from 52 to 91 bts in min with registered solitary supraventricular premature contractions (223 in total), paired supraventricular premature contractions (30 in total), episodes of atrial rhythm with duration of 8 complexes with HR

80 bts in min, no ST-segment elevation or depression episodes.

FINAL DIAGNOSIS

Acute Coronary Syndrome: circular STEMI (06-oct-2017). Trombolysis with tenecteplase (06-oct-2017). Coronary arteries atherosclerosis (coronary angiography 06-oct-2017) with PCI performed (right coronary artery stenting 06-oct-2017). Arterial hypertension III stage, II degree, very high risk. Heart failure by Killip I stage.

TREATMENT RECEIVED IN HOSPITAL

Clopidogrel 75 mg 1 time/day, aspirin 100 mg 1 time/day morning, eplerinone 25 mg 1 time/day, metoprolol 25 mg 2 times/day, enoxaparinum natrium 0,8 ml (80 mg) 2 times a day subcutaneously, pantoprazole 40 mg 2 times a day, atorvastatin 80 ml 1 time/day.

RECOMMENDATIONS

According to 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [1], the following recommendations may be applicable for our patient after discharge from hospital and for prevention of further STEMI episodes:

1. A reduction in chest pain after nitroglycerin administration is not recommended as a diagnostic manoeuvre in patient with suspected STEMI because of misleading results.

2. Early ambulation (day 1) is recommended in the majority of patients especially after using the radial access for PCI and low risk patients by PAMI-II criterias (age less than 70 years, left ventricle ejection fraction (LVEF) more than 45 %, one- or two-vessel disease, successful PCI, and no persistent arrhythmias). But for patients with extensive myocardial damage (as our patient is), heart failure, hypotension, or arrhythmias should be advised a prolongation of hospital stay.

3. Early echocardiography with LVEF assessment is indicated in all patients and it was done in our case. Medical therapy should include dual antiplatelet therapy (DAPT), anticoagulation, and secondary prevention therapies. DAPT, combining aspirin with low-dose (75–100 mg) and a P2Y12 inhibitor (clopidogrel is co-adjuvant of choice after fibrinolysis) is recommended for 12 months. In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy should be considered for 1–6 months. The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.

4. Secondary prevention: our patient is not obese, don't smoke and not an alchohol abuser but for STEMI patient is important to take part in an exercise-based cardiac rehabilitation programme which includes exercise training, risk factor modification, education, stress management, and psychological support.

5. As one of most important risk factors in patients with STEMI, high blood pressure, along with reduced salt intake, increased physical activity, should be pharmacologically controlled with a systolic blood pressure targets of < 120 mm Hg in patients at very high risk as our patient is.

In hemodynamically stable patients undergoing fibrinolysis oral beta-blocker initiation should be considered within the first 24 h. Lipid-lowering treatment should be started as early as possible, lipids profile advised being re-evaluated in 4–6 weeks after the ACS to determine whether the target levels have been reached and regarding safety issues. Routine use of calcium antagonists and nitrates in the acute phase is not indicated and showed no benefits. Treatment with ACE inhibitors was recommended in all STEMI patients with systolic LV dysfunction or heart failure, hypertension, or diabetes.

CONCLUSIONS

From one hand, in spite of side-effects of treatment as an increased risk of stroke and hemorrhagic stroke, prehospital FL is associated with a decreased risk of cardiogenic shock and its effectiveness depends on the time from symptom onset to reperfusion. From other hand, despite the fact that PPCI is the recommended default reperfusion strategy, its effectiveness depends also on time limits and absence of the majority of PPCI-facilated hospitals worldwide. Combination of prehospital single-bolus FL following after 3–24 h early routine angiography and PCI can improve post-STEMI survival and help to avoid hyperreactivity and thrombin-induced platelet activation after FL, which can be a key to success in effective treatment and rehabilitation after STEMI in patients without high risk factors of potential bleeding or stroke.

REFERENCES

1. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation / [B. Ibanez, S. James, S. Agewall, et al.] // European Heart Journal. – 2017. – No. 00. – p. 1–66.
2. Sutton A.G. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. / [A. G. Sutton, P. G. Campbell, R. Graham, et al.] // J Am Coll Cardiol. – 2004. – No. 44 (2). – p. 287.
3. Roule V. Prehospital fibrinolysis versus primary percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized controlled trials / [V. Roule, P. Ardouin, K. Blanchar, et al.] // Critical Care. – 2016. – No. 20. – p.359.
4. Jordan M. Improving door-to-needle times for patients presenting with ST-elevation myocardial infarction at a rural district general hospital / M. Jordan, J. Caesar // BMJ Quality Improvement Reports. – 2016. – No. 5. – p. 1–10.
5. Wang T. Y. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. / [T. Y. Wang, B. K. Nallamothu, H. M. Krumholz, et al.]. // JAMA. – 2011. – No. 305 (24). – p. 2540–2547.
6. Madan M. Relationship between time to invasive assessment and clinical outcomes of patients undergoing an early invasive strategy after fibrinolysis for ST-segment elevation myocardial infarction: a patient-level analysis of the randomized early routine invasive clinical trials. / [M. Madan, S. Halvorsen, C. Di Mario, et al.]. JACC Cardiovasc Interv. – 2015. – No. 8. – p. 166–174.

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CARDIOVASCULAR PATIENT WITH PERMANENT PACEMAKER DUE TO COMPLETE ATRIOVENTRICULAR BLOCK

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Permanent pacemaker implantation and medical therapy due to complete atrioventricular block and comorbid cardiac pathology are considered at an example of clinical case. Permanent pacemaker solved the problem of AV-block, however, drug therapy due to arterial hypertension, heart failure and dyslipidemia is not canceled and requires modification.

KEY WORDS: complete atrioventricular block, permanent pacemaker

СЕРЦЕВО-СУДИННИЙ ПАЦІЄНТ ІЗ ПОСТІЙНИМ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРОМ З ПРИВОДУ ПОВНОЇ АТРІОВЕНТРИКУЛЯРНОЇ БЛОКАДИ

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На прикладі клінічного випадку розглянуті можливість імплантації електрокардіостимулятора та медичної терапії з приводу повної атріовентрикулярної блокади і супутньої серцевої патології. Постійний кардіостимулятор вирішив проблему повної атріовентрикулярної блокади, однак лікарська терапія у зв'язку з артеріальною гіпертонією, серцевою недостатністю і дисліпідемією не відміняється і вимагає модифікації.

КЛЮЧОВІ СЛОВА: повна атріовентрикулярна блокада, постійний електрокардіостимулятор

СЕРДЕЧНО-СОСУДИСТЫЙ ПАЦИЕНТ С ПОСТОЯННЫМ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРОМ ПО ПОВОДУ ПОЛНОЙ АТРИОВЕНТРИКУЛЯРНОЙ БЛОКАДЫ

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На примере клинического случая рассмотрены возможность имплантации электрокардиостимулятора и медицинской терапии по поводу полной атриовентрикулярной блокады и сопутствующей сердечной патологии. Постоянный кардиостимулятор решил проблему полной атриовентрикулярной блокады, однако лекарственная терапия в связи с артериальной гипертонией, сердечной недостаточностью и дислипидемией не отменяется и требует модификации.

КЛЮЧЕВЫЕ СЛОВА: полная атриовентрикулярная блокада, постоянный электрокардиостимулятор

INTRODUCTION

Complete atrioventricular (AV) block occurs in patients with comorbid cardiac pathology [1–2]. Permanent pacemaker is sole method of treatment of the AV-block, however, it is requiring the control of drug therapy in connection with the change in hemodynamics [3–5].

This clinical case described below shows that pacemaker implantation in patient due to complete AV block is not canceling drugs support.

CLINICAL CASE

The patient L., a woman 46 years old was admitted to the cardiology department of the Kharkiv railway clinical hospital No1 of the branch «Center Of Healthcare» of public joint stock company «Ukrainian Railway» on the 6th of September 2017 with complaints of general weakness, dizziness, presyncope, shortness of

breath during physical activity (walking), disappearing after the rest, light palpitation, headaches in the occipital, parietal, frontal area, pressing character, periodic, arising during excitement, physical exertion.

ANAMNESIS MORBI

In 2009, she was diagnosed with neurocirculatory dystonia, in 2015 – arterial hypertension 2nd stage 1st grade (max blood pressure (BP) 147/97 mm Hg; usual BP 135/85 mm Hg), ramipril 2.5 mg was taken from time to time. In 2016 – AV-block second degree (Obits II), in 2017 – complete AV block was diagnosed on a doctor's visit after complains of severe palpitation and electrocardiography (ECG) (see pic. 1). After consulting with the physician and ECG monitoring patient was referred to pacemaker implantation.

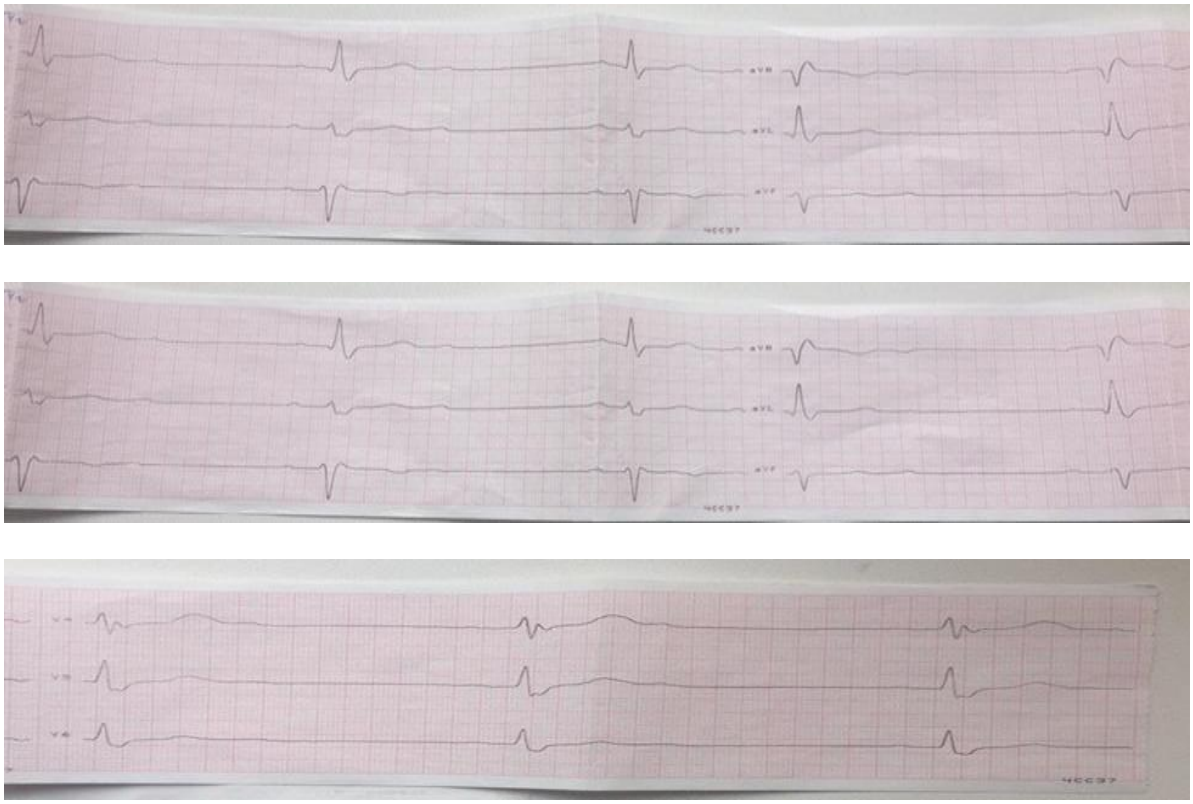

Fig. 1 Complete AV block, heart rate 35 bpm, sinus atrial rhythm, PR interval irregular

ANAMNESIS VITAE

Childhood infections, injuries, tuberculosis, sexually transmitted diseases were denied by patient. No family history of any endocrine or cardiac disorders. Allergic history is not burdened. Patient denies smoking, do not abuse alcohol.

OBJECTIVE EXAMINATION

General condition of the patient was satisfactory, consciousness – clear, state – severe, body position – active. Emotionally stable and in an optimistic mood. Height = 168 cm, weight = 100 kg, BMI = 37.3 kg/m^2. Temperature – 36.7°C.

Skin is normal colored, without any scars, visible mucous membranes are pale pink and clean. Mucous membranes are pale and wet. Tongue – clear and wet.

Peripheral lymph nodes are not palpable. The thyroid is not palpable, signs of eyelid retraction, periorbital edema, proptosis are absent.

Joints are normal, active and passive movements are not painless.

Respiratory system: the chest is hypersthenic, normal respiratory effort with no use of accessory muscles. Palpation - normal tactile fremitus. Percussion – no clinically significant changes. Auscultation – vesicular breathing, no added sounds. Breathe rate – 20 per min.

Cardiovascular system: no jugular vein distention. Carotid, radial, posterior tibialis, and pedal pulses 2 + symmetric, no edema. Apex beat localized in the 5th intercostal space, diffuse. Percussion: heart borders extended to the left on 1,5 cm of midclavicular line. Auscultation: regular S1, S2, normal rhythm, no murmur, rub, or gallop. BP in left hand = 145/100 mm Hg, BP in right hand = 140/95 mm Hg, HR = pulse = 35 bpm (before pacing).

Gastrointestinal system: abdomen is soft, painless, symmetrical, no discrepancies of the abdominal muscles, no visible peristalsis, liver edge is smooth, painless, palpated 0.5 cm below the costal arch, spleen and pancreas are not palpable, stool and diuresis were unremarkable.

Urogenital and sexual systems: Pasternatsky sign is negative. Menopause during 1 year.

LABORATORY AND INSTRUMENTAL TESTS

Complete blood count, urine and biochemical analysis (07/09/17) were in normal ranges.

Lipid profile (07/09/17) revealed type IIa dyslipidemia according to Frederickson's phenotype (total cholesterol = 5.29, LDL = 3.75, atherogenic coefficient = 3.33).

ECG 2 days after pacemaker implantation (09/09/17): complete AV block, sinus atrial rhythm, PR interval regular, RR > PP. Esprit DDD pacemaker: there is 100 % ventricular capture – a QRS complex follows each ventricular pacing spike; no atrial pacing spikes are seen; HR – 65 bpm, stimulation threshold - 0,75 V, impedance – 350 Om (see pic. 2).

Echocardiography (06/09/17): left ventricular hypertrophy (LVH), signs of increasing diastolic stiffness of the LV wall.

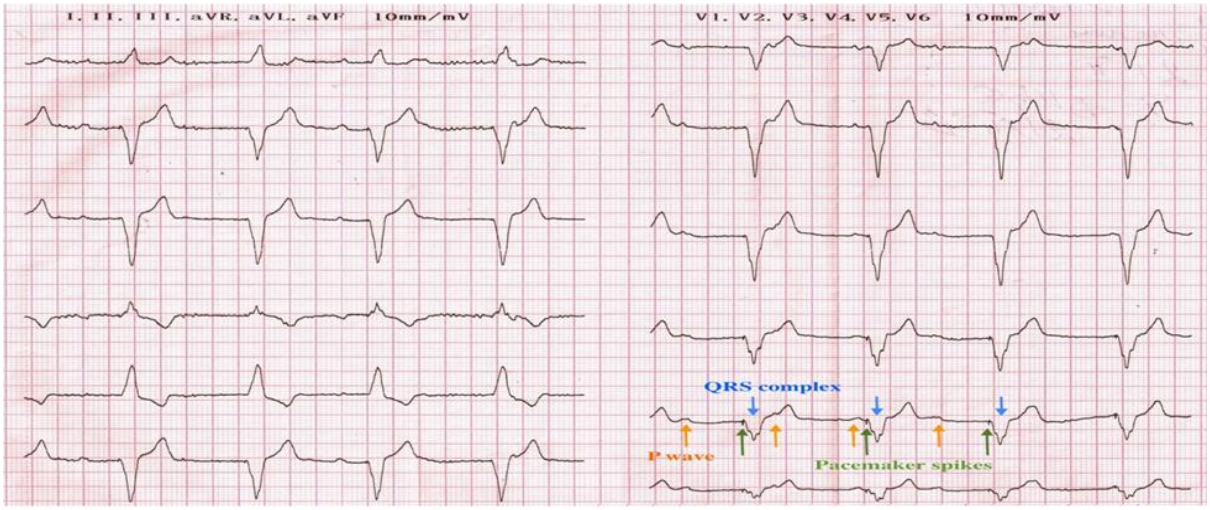

Fig. 2 Condition after cardiac pacemaker implantation (DDDR) due to complete AV block

CLINICAL SYNDROMES

- Conduction disorder
- Arterial Hypertension
- Heart failure
- Dyslipidemia
- Obesity

CLINICAL DIAGNOSIS

Main: Ischemic heart disease, condition after cardiac pacemaker implantation (DDDR) due to complete AV block, essential arterial hypertension IInd stage, 1st grade, hypertensive heart (LVH), heart failure II B, II FC with preserved ejection fraction (EF – 65 %), dyslipidemia II a type (after Fredrickson) and moderate added total CV risk.

Comorbidity: Obesity II degree.

RECOMMENDATION AND TREATMENT

Lifestyle modification:

– reducing the weight by 5–10 %, 150 min/week of moderate-intensity exercise (eg, brisk walking) plus flexibility and strength training;

– eat regular meals and snacks, avoid fasting;

– consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants);

– use mild cooking techniques instead of high-heat cooking.

Surgical therapy:

Control pacemaker parameters after 1, 6 months and 1 year (condition after DDD mode pacing, 9th of September 2017).

Medicament therapy:

– Antiplatelet – Cardiomagnyl 75 mg once daily in the evening;

– Angiotensin receptor blocker – Telmisartan 40 mg once daily in the morning;

– Statin – Atorvastatin 40 mg once daily in the evening.

CONCLUSIONS

Permanent pacemaker solved the problem of AV-block, however, drug therapy due to arterial hypertension, heart failure and dyslipidemia is not canceled and requires modification.

REFERENCES

1. Socie, Pierre et al. «Frequency Of Recovery From Complete Atrioventricular Block After Cardiac Surgery». The American Journal of Cardiology 120.10 (2017): 1841–1846. Web. 25 Jan. 2018.
2. Liao, Jo-Nan et al. «Long-Term Outcome in Patients Receiving Permanent Pacemaker Implantation for Atrioventricular Block: Comparison of VDD and DDD Pacing». Ed. Heye Zhang. Medicine 95.35 (2016): e4668. PMC. Web. 25 Jan. 2018.
3. Brignole, M. et al. «2013 ESC Guidelines On Cardiac Pacing And Cardiac Resynchronization Therapy: The Task Force On Cardiac Pacing And Resynchronization Therapy Of The European Society Of Cardiology (ESC). Developed In Collaboration With The European Heart Rhythm Association (EHRA) ». Europace 15.8 (2013): 1070–1118. Web. 13 Jan. 2018.
4. Klein, Helmut U., Ilan Goldenberg, and Arthur J. Moss. «Risk Stratification For Implantable Cardioverter Defibrillator Therapy: The Role Of The Wearable Cardioverter-Defibrillator». European Heart Journal 34.29 (2013): 2230–2242. Web. 25 Jan. 2018.
5. Brunacci, Michele et al. «Two Hearts Synchronized Each Other With A DDD Pacemaker». Journal of Cardiovascular Medicine 17 (2016): e239–e240. Web. 25 Jan. 2018.

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BACTERIAL INVASION AS A KEY FACTOR IN PROGRESSION OF REACTIVE ARTHRITIS ON EXAMPLE OF CLINICAL CASE

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A clinical case of middle age male diagnosed with reactive arthritis developed on the background of multiple bacterial invasions such as Salmonella enterica, Ureaplasma urealyticum, Mycoplasma hominis, Borrelia burgdorferi sensu lato and characterized by chronic persistent course of the disease with destructive-inflammatory changes in the joints. This case illustrates the influence of bacterial pathogens on the course and the progression of reactive arthritis.

KEY WORDS: reactive arthritis, bacterial infections, chronic arthritis

БАКТЕРІАЛЬНА ІНВАЗІЯ, ЯК КЛЮЧОВИЙ ФАКТОР У ПРОГРЕСУВАННІ РЕАКТИВНОГО АРТРИТУ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Клінічний випадок реактивного артриту у чоловіка середнього віку, який розвинувся на тлі багаторазових бактеріальних інвазій таких як Salmonella enterica, Ureaplasma urealyticum, Mycoplasma hominis, Borrelia burgdorferi sensu lato, та характеризувався хронічним стійким перебігом захворювання з деструктивно-запальними змінами в суглобах. Цей клінічний випадок іллюструє вплив бактеріальних патогенів на перебіг та прогресування реактивного артриту.

КЛЮЧОВІ СЛОВА: реактивний артрит, бактеріальні інфекції, хронічний артрит

БАКТЕРИАЛЬНАЯ ИНВАЗИЯ КАК КЛЮЧЕВОЙ ФАКТОР В ПРОГРЕССИРОВАНИИ РЕАКТИВНОГО АРТРИТА НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Клинический случай реактивного артрита у мужчины среднего возраста, который развился на фоне многократных бактериальных инвазий, таких как Salmonella enterica, Ureaplasma urealyticum, Mycoplasma hominis, Borrelia burgdorferi sensu lato и характеризовался хроническим персистирующим течением заболевания с деструктивно-воспалительными изменениями в суставах. Этот клинический случай иллюстрирует влияние бактериальных патогенов на течение и прогрессирование реактивного артрита.

КЛЮЧЕВЫЕ СЛОВА: реактивный артрит, бактериальные инфекции, хронический артрит

INTRODUCTION

Reactive arthritis (ReA) is a condition associated with bacterial infections of the urogenital and gastrointestinal tract, which trigger the onset of the disease, and also play a role in the progression of pathological processes in the musculoskeletal system [1–2].

Reactive arthritis (formerly known as Reiter disease) is characterized as a sterile inflammation of the synovial membrane, tendons and fascia triggered by an infection on a distant site, usually gastrointestinal (GI) or urogenital [1].

It is frequently associated with the human leukocyte antigen (HLA-B27) haplotype and is classified in the category of seronegative spondyloarthropathies. It predominantly affects young adults in the 20–40 age groups, men more than women (ratio 3:1) [3]. ReA has been

associated with gastrointestinal (GI) infections often caused by Shigella, Salmonella, Campylobacter, as well as with genitourinary (GU) infections (Chlamydia Trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum) and others. Adolescents and young men are most likely to develop ReA after a genitourinary infection, whereas young children tend to have the postdysenteric form [4]. The mechanism by which the interaction of the inciting organism with the host leads to the development of ReA is not known. There are several pathogenetic theories that include [4]:

- Molecular mimicry theory (similarity exists at the molecular level between the HLA-B27 molecule and the inciting organisms, allowing the triggering of an immune response);
- Role of HLA-B27 as a receptor for certain bacteria;
- Defective class I antigen-mediated cellular response (HLA-B27 molecule may be a defective molecule associated with an aberrant cytotoxic T-cell response).

The clinical picture of reactive arthritis ranges from a mild localized condition to a severe multisystem lesions. Involvement of the joints varies from a transient monoarthritis to a widespread polyarthritis involving the peripheral and axial joints with or without characteristic extra-articular lesions, particularly enthesopathy, psoriasiform mucosal, and cutaneous lesions, inflammatory eye disease, and cardiovascular lesions [3]. The onset is usually acute and characterized by malaise, fatigue, and fever. It usually develops 1–4 weeks after a genitourinary (GU) or gastrointestinal (GI) infection. A history or evidence of recent infection is critical to the diagnosis.

The classic triad of symptoms (noninfectious urethritis, arthritis, and conjunctivitis) is found in only one third of patients with ReA and has a sensitivity of 50.6 % and a specificity of 98.9 % [5].

Articular lesions are characterized as asymmetrical, predominantly lower-extremity arthritis with redness, swelling, pain and warmth in and around the affected joint; it is distributed primarily in feet, ankles, knees, sacroiliac joints; hands, hips, and spine are less frequently involved. Dactylitis with so called «sausage digits» may develop. Enthesopaties are important feature of ReA and can be seen in near 30 % of cases; enthesitis is usually described as tenderness, with or without swelling at the sites of tendon or fascial attachments, especially the Achilles tendon and plantar fascia attachments to the calcaneum [1]. Urogenital symptoms may be primary or postdysenteric and may include initial nongonococcal urethritis, with frequency, dysuria, urgency, and urethral discharge; cystitis, prostatitis, vulvovaginitis, cervicitis, salpingo-oophoritis and circinate balanitis (balanitis circinata) consisting of small shallow painless ulcers of the urethral meatus or the glans penis which is characteristic feature of reactive arthritis. Eye lesions often are presented as conjunctivitis, reactive iritis, episcleritis, veitis; ophthalmologic symptoms may include erythema, burning, tearing, photophobia, pain, and decreased vision.

Lesions of skin and mucosae include keratoderma blennorrhagicum, hyperkeratosis, onychodystrophy, psoriasis-like skin lesions, erosions of lips, tongue, cheeks mucosae. Cardiovascular involvement usually is rare; it can be presented as myocarditis, endocarditis, seldom – as aortitis with subsequent aortic insufficiency.

Diagnostics of reactive arthritis is based on the recognition of the typical clinical features of spondyloarthropathy and evidence of urogenital infection (symptoms and signs of urethritis and microscopic confirmation by a Gram-stained urethral smear; mucopurulent cervicitis in women) or gastrointestinal infections (stool culture).

Essential investigations include: full screening for sexually transmitted infections (STIs), including HIV; gastrointestinal infections; full blood count and acute phase response panel; urinalysis (to check for renal pathology); synovial fluid analysis which is usually used in cases where septic arthritis is suspected. Often used investigations are: HLA-B27 analysis; X-rays of affected joints, spine, sacroiliac joints, ultrasonography of affected joints, entheses; electrocardiogram (ECG), ophthalmic evaluation including slit lamp assessment, liver and kidney function tests [1].

There is no specific treatment for reactive arthritis. Treatment options include lifestyle modifications with restriction of physical activity, especially weight-bearing activity in acute period with further physiotherapy after improvement of symptoms [1]. Essential is to identify and treat triggering infections: antimicrobial therapy for infection identified –

macrolides, tetracyclines, fluoroquinolones are considered as the most effective [1, 6]. As symptomatic therapy are used NSAIDs and corticosteroids. Sulphasalazine, methotrexate are indicated in severe cases where disabling symptoms persist for three or more months.

Prognosis varies but typically reactive arthritis has a self-limited course, with resolution of symptoms by 3–12 (usually 4–6) months. The presence of HLA-B27 and infections triggered by Yersinia, Salmonella, Shigella, Chlamydia may predict a more prolonged course and severe outcome. A fatal outcome is seldom reported. ReA has a high tendency to recur (15–50 % of cases), particularly in HLA-B27 – positive patients. A new infection or other stress factor could cause reactivation of the disease. About 15–30 % of patients with ReA develop a long-term, sometimes destructive, arthritis or enthesitis or spondylitis [4].

OUR CASE

Male patient, 43 years old complains of dull pain in the knee, ankle, hip joints, in the cervical, lumbosacral spine, morning stiffness of the joints for 2,5 to 3 hours. The pain is permanent, more pronounced in the right knee and right hip joints, worsens with movements, decreases with the intake of NSAIDs (diclofenac).

Also patient complains on swelling and pain in his left wrist that worsens when he fists his hand.

Anamnesis of the disease. The patient considers himself ill from July 2010 when 2 weeks after suffering Salmonellosis first acutely appeared pain in the right knee, ankle joints, lower back pain, right heel pain and burning, redness of both eyes. Patient denied the presence of urethritis. He did not seek medical help, occasionally took NSAIDs. In November 2010 joint pain worsened, right hip become affected; after referral to a rheumatologist, he was admitted to Kharkiv hospital #28, where high titers of mycoplasma and ureaplasma were detected (ELISA and PCR). Was made the diagnosis of urogenital reactive arthritis and he was treated with doxycyclin, NSAIDS, dexamethasone. His state has improved but still there was moderate pain and slight limitation of joint mobility. He continued treatment under the supervision of rheumatologist but his symptoms persisted and in 2011 after inpatient treatment the diagnosis of chronic reactive arthritis was made. In December 2012 the patient tried to «increase the immunity» by eating raw eggs and was hospitalized with diagnosis: Salmonellosis, associated with *Salmonella enterica*, serovar Paratyphi B variant Java, gastroenterictis of moderate severity (17.12.2012–25.12.2012). Subsequently he had hospitalization with diagnosis: Lime's disease (associated with Borrelia burgdorferi sensu lato), chronic course (26.12–15.01.13). After this the patient's state worsened significantly – intensified pain in affected joints with enlargement, redness, restriction of movements; also become affected left wrist joint, temperature increased up to 37,4°C. In January 2013 he had inpatient treatment in rheumatology department with the diagnosis: Reactive arthritis, chronic course, activity of 2 grade, polyarthritis, right-sided sacroiliitis 2d grade, functional impairment of 2 degree. The patient was treated with methotrexate, sulphasalazine. Subsequently, the patient was annually hospitalized in a rheumatology department.

Anamnesis of life. Patient is not working, denies smoking, alcohol and drug abuse. Postponed diseases: URVI, tonsillectomy at the age of 9 years. He denies viral hepatitis, tuberculosis, AIDS. Had no traumas, surgeries, allergic reactions.

Objective examination. General state of the patient is of moderate severity due to his articular status. Patient is oriented to the time, place, himself. He uses a cane for walking; Tredelenburg gait is present. Height – 191 cm weight – 90 kg, BMI – 24.7 kg/m2; t – 36,8°C. Skin: pale, clean; skin turgor, moistness is preserved; visible mucous membranes are clean, moist; subcutaneous adipose tissue is developed moderately, distributed symmetrically. Lymphatic nodes are not palpable. No edemas. Thyroid gland is not enlarged. Lungs: resonance percussion sound, vesicular breathing over both lungs fields, RR – 17 per minute. Heart borders on percussion are not enlarged, heart tones are clear, loud, rhythmic; BP dex – 129/85, BP sin – 130/85, radial pulse is synchronous, rhythmic at 88bpm. Abdomen is painless on superficial and deep palpation in all regions. Liver at the costal margin, painless; spleen is not palpable. Pasternatskiy sign is negative on both sides. Urination is free, painless.

Musculo-skeletal system examination. Left wrist is moderately swollen, slightly

painful on palpation and when the patient fists his hand; there is no increased skin temperature or skin color changes. Vertebral column: scoliotic posture; spine mobility: Schober test - 15 cm. Pelvis and hip joints: there is a right lateral pelvic tilt; Tredelenburg gait is present; pelvis compression tests are positive on the right side. Knee joints: smoothness of the contours, edema, crepitation during movement more pronounced in the right knee, increased skin temperature above the right knee joint. Ankle joints: smoothness of contours, puffiness, more pronounced on the right, tenderness in palpation with slight restriction of movements; there are signs of Achilles tendinitis. Range of movements (table)

Table

Range of movements in joints

Type of movement	Hip joints	Knee joints	Ankle joints
Flexion (flex)	Right: 120°, left: 110°	Right: 90°, left: 90°	Right: 120°, left: 120°
Extension (ext)	Right: 150°, left: 160°	Right: 160°, left: 170°	Right: 80°, left: 80°
Normal range (ext/flex)	180°/75°	180°/40°	70°/130°

The results of current patient's investigations: full blood count: increased ESR: 38 mm/h (N – 2–15 mm/h); urinalysis, fasting plasma glucose, liver function tests, kidney function tests – all parameters within the normal range; acute phase response panel: increased CRP: 12 (N – <5), seromucoid: 5,9 S-H (N – 1–5 S-H); serological tests: positive ANA (antinuclear antibodies), HLA-B27 was negative. Blood analysis for urogenital infections: PCR (polymerase chain reaction): DNA of Ureaplasma urealyticum, Mycoplasma hominis is detected; ELISA (enzyme-linked immunosorbent assay): Mycoplasma hominis IgG – 2,623 *(positive)*, Ureaplasma urealyticum IgG – 0,941*(positive)*. Microprecipitation test of blood serum for syphilis, HIV test – negative. ECG: sinus rhythm with HR – 74, electric axis of the heart – normal position, no pathological changes. X-ray of cervical spine in lateral flexion: height and structure of intervertebral spaces is not changed, compaction, uneven deflection of the closure plates in the articular joints. Conclusion: initial signs of spondylarthrosis. X-ray of knee joints: moderately pronounced uneven joint space narrowing (JSN), subchondral sclerosis, thickening of soft tissues more pronounced on the right. Conclusion: bilateral gonarthrosis of 2nd degree. X-ray of ankle joints: thickening of the joint capsule, articular cleft not altered. X-ray of sacroiliac and hip joints (Figure 1): Moderately pronounced uneven joint space narrowing (JSN) of the right sacroiliac joint, subchondral sclerosis, marginal erosions of the closure plates; hip joints – significant JSN of both joints more pronounced on the right side, subchondral sclerosis, osteophytes, areas of destruction of the head of the right femur. Conclusion: signs of coxarthrosis – right-sided – 4 degree, left-sided – 3 degree, right-sided sacroiliitis 2 degree, aseptic necrosis of the head of the right femur. Right lateral pelvis tilt (vertical axis – 4,5°, horizontal axis – 3°).

Consult of orthopedist-surgeon: right-sided coxarthritis 3–4degree; persistent severe pain syndrome; hip replacement is recommended.

Diagnosis: Reactive arthritis (since 2010) associated with urogenital infection (ureaplasmosis, mycoplasmosis), chronic continuously-relapsing course, 2nd grade of activity, polyarthritis with knee joints lesions (bilateral gonarthrosis of 2nd degree), ankle joints lesions, hip joints lesions(right-sided coxarthrosis 4th grade, left-sided – 3^{d} grade) , unilateral right-sided sacroileitis 2^{d} grade, functional impairment 2 degree. Disability 3^{d} degree.

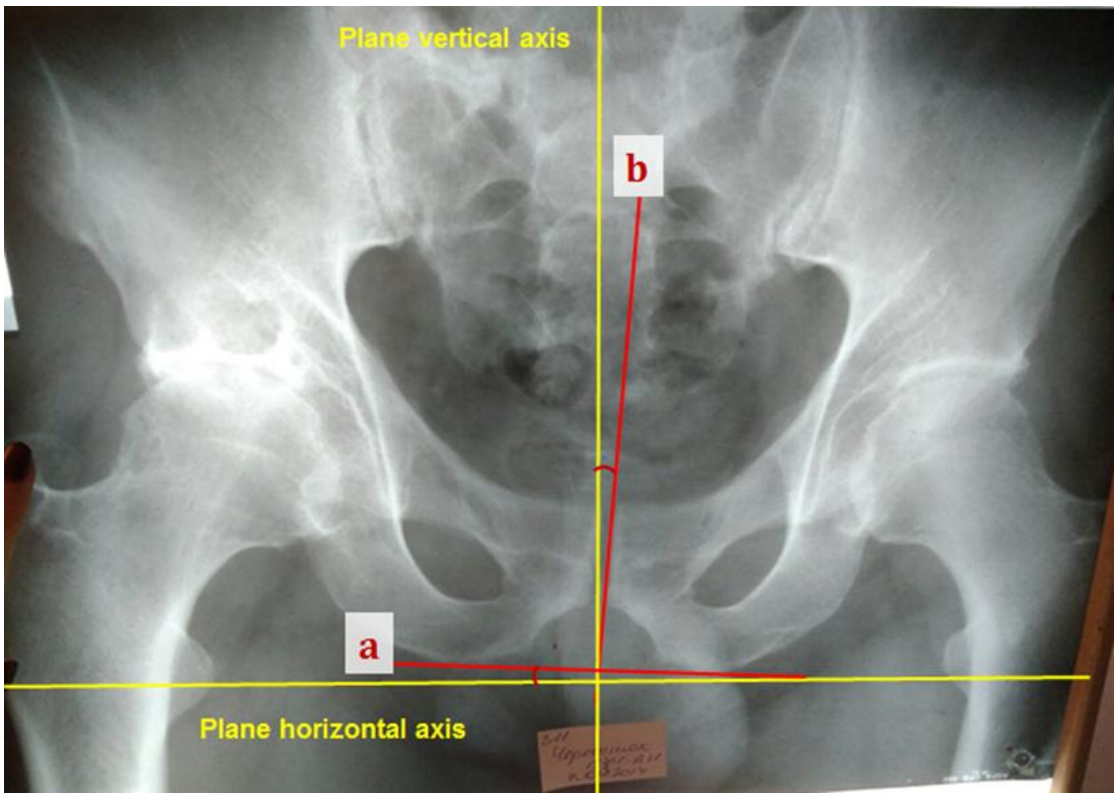

Fig. 1. X-ray of sacroiliac and hip joints; a – horizontal axis of the pelvis, b – vertical axis of the pelvis

Treatment plan. Physical activity under the supervision of a physical therapist; avoid overcooling, insolation. Drug therapy: metotrexate 10 mg per week continuously; folic acid 5 mg per day – next day after metotrexate; diclofenac sodium 75 mg 2 times per day; methylprednizolone 8 mg per day continuously; hondroitine-sulphate 500 mg twice daily 1month; calcium and D3 – combined preparation (calcium carbonate 1250 mg, chole-calciferol (vitamin D3) – 10 μg (400 IU)) 1 tab 2 times per day for 2 months.

Surgical intervention – right hip replacement is recommended.

DISCUSSION

The etiologic factor in the development of reactive arthritis remains the subject of discussion mainly due to the fact that in addition to known pathogens such as Trichomonas, Escherichia or serotypes of Salmonella with proved influence on the occurrence of reactive arthritis [1–4, 7–9] role of such pathogens as Mycoplasma and Borrelia remains controversial. It is known [1–4, 7–8] that Salmonella (and in particular Salmonella enterica serovars Typhimurium enteritidis, Paratyphi B and C, and others) is a triggering agent for the development of reactive arthritis. Incidence of reactive arthritis due to Salmonella varies up to 14 %, and according to some data – up to 30 %, depending on the type of Salmonella [2, 8–9]. In addition, it was found that Salmonella infection correlated with a sufficiently high risk of chronic course of the disease: thus, according to a 20-year study [2], Salmonella induced chronic reactive arthritis was observed in 19 % of cases. The role of Ureaplasma urealyticum in the development of reactive arthritis is also confirmed [1, 9–12]. According to the studies [13], Ureaplasma urealyticum was found in 26.6 % of patients with reactive arthritis. However, most often there is a mixed infection, while ureaplasma monoinfection is detected in minority of cases [9].

The influence of Mycoplasma hominis and Borrelia burgdorferi on the development of reactive arthritis is controversial. These pathogens for a long time were not ranked among the infectious agents associated with reactive arthritis [14]. However, some

researchers [2, 15] indicate a link between infection with these microorganisms and reactive arthritis, identifying them in a separate group of probable potential agents. While according to [9, 11–12, 16–17], Mycoplasma hominis infection and the chronic infection caused by Borrelia burgdorferi are considered as a trigger factor for the development of reactive arthritis.

The course of reactive arthritis in our patient was associated with such infectious agents as Salmonella enterica, Ureaplasma urealyticum, Mycoplasma hominis, Borrelia burgdorferi sensu lato; the presence of several bacterial pathogens, as well as re-infection with Salmonella, had a significant effect on the formation of resistance of autoimmune disorders and, as a consequence, a pronounced inflammatory response.

The analysis of the patient's ESR dynamic changes from the moment when the diagnosis was made in 2010 till 2017 confirms this (Figure 2).

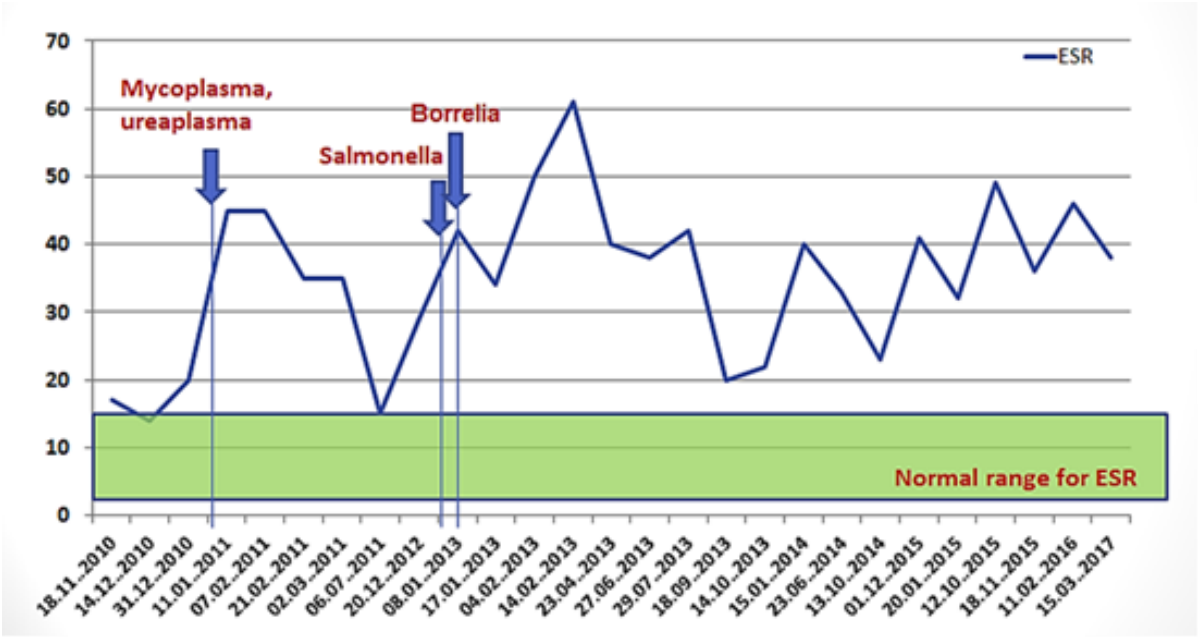

Fig. 2. Correlation between bacterial invasions and dynamic changes of ESR (2010–2017 yrs)

An increase in ESR above 30 mm/h, hip joints involvement, unresponsiveness to nonsteroidal anti-inflammatory drugs, lumbar spine stiffness, dactylitis, and the onset of the disease before the age of 16 are considered to be the factors affecting the chronicity of the disease which is usually observed in 15–30 % of patients with ReA [3–4].

The course of reactive arthritis in our patient was characterized by persistent pain and joints inflammation with involvement of hip joints and the absence of a long-term positive effect from NSAIDs therapy, a steady increase in the inflammatory markers and ESR. Progression of the disease correlated with episodes of repeated infections (see Figure 2), which led to the chronicity of the pathological process and, as a result, to destructive articular changes, a sharp deterioration in the quality of life and the need for surgical treatment.

Thus, this clinical case confirms the important role of bacterial infections in the pathogenesis of reactive arthritis, and gives new information about influence of several pathogens on the course and the progression of the disease.

CONCLUSIONS

In our patient, reactive arthritis was characterized by a chronic persistent course with a constant increase in inflammatory markers and destructive-inflammatory changes in the joints.

An important role in the progression of reactive arthritis in this patient played multiple bacterial invasions, which were not only a trigger of the onset of the disease, but also

maintained a chronicity of the pathological processes.

This clinical case is an illustration of the fact that infectious bacterial diseases play a key role in the pathogenesis of reactive arthritis, and repeated bacterial infections affect the course and progression of the disease, which leads to a significant disruption of the function of the musculoskeletal system.

It is important to treat the patient with avoidance of polypharmacy; this goal is achieved by the appointment of several basic drugs and a supportive therapy used in courses.

REFERENCES

1. Carlin E.M. 2014 European Guideline on the management of sexually acquired reactive arthritis/ E.M. Carlin, J.M. Ziza, A. Keat [et al.] // International Journal of STD & AIDS. – 2014. - Vol. 25 (13). – p. 901–912.
2. Colmegna I. HLA-B27-Associated Reactive Arthritis: Pathogenetic and Clinical Considerations / I. Colmegna, R. Cuchacovich, L. R. Espinoza // Clinical microbiology reviews. – 2004. - Vol. 17 (2). – p. 348–369.
3. Hamdulay S. S. When is arthritis reactive? / S. S. Hamdulay**,** S. J. Glynne, A. Keat // Postgrad Med J. – 2006. – Vol.82 (969). – p. 446–453.
4. Reactive arthritis. [electronic resource]/ [C. J. Lozada, M. F. Carpintero, R. A. Schwartz] // Medscape. – 2017. – Access to resourse: https://emedicine.medscape.com/article/331347-overview.
5. Wu I. B. Reiter's syndrome: the classic triad and more. / I. B. Wu, R. A. Schwartz // J Am Acad Dermatol. – 2008. – No. 59 (1). – p. 113–21.
6. Nomenklatura, klasifikacija, kriteriï diagnostiki ta programi likuvannja revmatichnih hvorob. / Pod red. V. M. Kovalenko, N. M. Shuba // Kiïv. – 2004. – s. 117–119.
7. Tuompo R. Reactive arthritis following Salmonella infection: a population-based study. / R. Tuompo, T. Hannu, L. Mattila [et al.] // Scandinavian Journal of Rheumatology. – 2013. – Vol. 42 No. 3. – p. 196–202.
8. Ekman P. Modification of disease outcome in salmonella-infected patients by HLA–B27 / P. Ekman, J. Kirveskari, K. Granfors // Arthritis & Rheumatism. – 2000. – Vol. 43 No. 7. – p. 1527–1534.
9. Spas'ka G.O. Reaktivnij artrit: suchasnij poglyad na problem. / G.O. Spas'ka // Ukraïns'kij medichnij chasopis. – 2011. – No. 6 (86). – S. 42–48.
10. Horowitz S. Ureaplasma urealyticum in Reiter's syndrome. / S. Horowitz, J. Horowitz, D. Taylor-Robinson // The Journal of Rheumatology. – 1994. – No. 21 (5). – p. 877–882.
11. Butrimiene I. Potential triggering infections of reactive arthritis./ I. Butrimiene, J. Ranceva, A. Griskevicius // Scand J Rheumatol. – 2006. – No.35 (6). – p. 459–462.
12. Vorushilina I. E. Tetrada priznakov pri bolezni Rejtera: klinicheskoe nablyudenie. / I. E. Vorushilina, M. I. Mazharova, A. V. Odinec // Medicinskij vestnik severnogo kavkaza. – 2011. – No. 2. – p. 88–90.
13. Bolezn' Rejtera: sovremennye podhody k lecheniyu. [electronic resource] / [G. M. Bondarenko] // Dermatovenerologiya. – 2009. – Access to resourse: https://kiai.com.ua/ru-issue-article-271/Bolezn-Reytera-sovremennye-podhody-k-lecheniyu.
14. Taylor-Robinson D. The association of Mycoplasma hominis with arthritis. / D. Taylor-Robinson, B. J. Thomas, P. M. Furr [et al.]// Sex Transm Dis. – 1983. – No. 10 (4). – p. 341–344.
15. Sibilia J. Reactive arthritis or chronic infectious arthritis? / J. Sibilia, F-X. Limbach // Ann Rheum Dis. – 2002. – No. 61. – p. 580–587.
16. Sukumar Mukherjee Reactive Arthritis: Current Perspectives. / Mukherjee Sukumar, Kar Madhuchanda // Journal, Indian Academy of Clinical Medicine. – 2000. – Vol. 1 No. 3. – p. 233–238.
17. Weyand Cornelia M. Immune responses to Borrelia burgdorferi in patients with reactive arthritis / Cornelia M. Weyand, Jorg J. Goronzy // Arthritis & Rheumatism. – 1989. – Vol. 32 No. 9. – p. 1057–1064.

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CLINICAL CASE OF GENERAL SOMATIC COMPLAINTS IN 47 Y.O. FEMALE

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A clinical case of general somatic complaints in 47 y.o. female, presenting for several years has described. Patient F., presents with uncertain complaints of general character – tiredness, general weakness, loss of energy. During the biennium was examined and treated by gynecologist, endocrinologist, cardiologist, gastroenterologist with no benefit. Anamnesis vita is significant for uterine fibroid. After thorough interviewing was found that patient was done ECG, EchoCG, gastroscopy, thyroid tests but no CBC, urinalysis, general biochemical panel during this two years. The CBC results were stunning and gave answers to all questions.

KEY WORDS: clinical case, anemia, complete blood count

КЛІНІЧНИЙ ВИПАДОК ЗАГАЛЬНОСОМАТИЧНИХ СКАРГ У ПАЦІЄНТКИ 47 РОКІВ

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Описано випадок загальносоматичних скарг у пацієнтки 47-річного віку, що турбували протягом декількох років. Пацієнтка Ф., скаржиться на загальну слабкість, втомлюваність, втрату енергії. Протягом двох років зверталася до гінеколога, ендокринолога, кардіолога, гастроентеролога, була обстежена цими спеціалістами. Призначене лікування виявилося неефективним. Багато років страждає на фіброміому матки і з цього приводу щорічно відвідує гінеколога. Після ретельного опитування було виявлено, що за ці роки пацієнтці було зроблено ЕКГ, УЗД серця, гастроскопію, визначення рівня гормонів щитовидної залози у крові, але жодного клінічного аналізу крові, сечі або загального біохімічного. Перші ж результати клінічного аналізу крові були приголомшливі та одразу дали відповіді на всі питання.

КЛЮЧОВІ СЛОВА: клінічний випадок, анемія, клінічний аналіз крові

КЛИНИЧЕСКИЙ СЛУЧАЙ ОБЩЕСОМАТИЧЕСКИХ ЖАЛОБ У ПАЦИЕНТКИ 47-МИ ЛЕТ

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Описан случай общесоматических жалоб в течение нескольких лет у пациентки 47-летнего возраста. Пациентка Ф., жалуется на общую слабость, утомляемость. В течение двух лет обращалась к гинекологу, эндокринологу, кардиологу, гастроэнтерологу, была обследована этими специалистами. Назначенное лечение оказалось неэффективным. В анамнезе жизни - фибромиома матки, в связи с чем ежегодно посещает гинеколога. После тщательного опроса было выявлено, что за эти годы пациентке было проведено ЭКГ, УЗИ сердца, гастроскопия, определение уровня гормонов щитовидной железы в крови, но не выполнено ни одного клинического анализа крови, мочи или общего биохимического исследования. Первые же результаты клинического анализа крови сразу дали ответы на все вопросы.

КЛЮЧЕВЫЕ СЛОВА: клинический случай, анемия, клинический анализ крови

INTRODUCTION

With age the comorbidity problem becomes more pressing issue [1-2]. It seems difficult to interpret complaints such as fatigue, general weakness, malaise because of their uncertainty and inability to determine at a glance problem with which body system produce them.

Specialized doctors tend to interpret such complaints in favor of «their» diagnosis, which, in some cases, prevents them to see the whole problem and treat effectively.

We present the clinical case of general somatic complaints in middle age woman, presenting for several years. Patient was examined and treated by four specialized doctors without significant effect, and finally it ended up in banal cause.

CLINICAL CASE

Patient F., female, 47 y.o., complains of tiredness, general weakness, low energy, heaviness in the legs. Also reports dyspnea and tachycardia with low physical exertion, dizziness in the metro. Heart intermissions, chest pain, cough denies. She also denies edema but reports face and legs puffiness. Her BP varies between 100–110/70 mm Hg, but sometimes, mostly after menstruation, falls up to 70/40 mm Hg. Low BP accompanied with light dizziness but not affects the ordinary activity. Review of digestive system revealed the lack of appetite. Review of urinary system was significant for periodical imperative urge to urinate without any evident provoking factor. Urination is painless, of ordinary frequency. No changes in urine volume or color. Pain in the lumbar region denies. Menstrual periods are regular, 23 days, bleedings are painless, 2–3 days, not heavy. Since 2008 to 2012 had scanty bleedings between menstruations, now bleedings between menstruations denies. Review of musculoskeletal system was unremarkable. Reports slight reduction in work capacity.

Presenting complaints of tiredness and general weakness gradually increased over 2 years. In January 2017 occurred dyspnea, dizziness, uncertain pain in the abdomen. 19.01.2017 was examined by gastro-enterologist. After ultrasound of the abdominal cavity (19.01.2017) and gastroscopy (19.01.2017) the diagnosis of gastropathy, cholecystopathy, micronephrolithiasis was made. Mebeverinum and pancreatinum was admitted for 10 days, with no effect. In May 2017 dyspnea and dizziness became more prominent. Sense of heaviness in the legs, face puffiness occurred. 05.05.2017 was examined by cardiologist. The diagnoses of cardiopsychoneurosis, mitral valve prolapse of 2^{nd} degree, HF 0 was made. Patient was treated with «Detralex», asparaginat K-Mg and trimetazidine, with short and insignificant effect. A tentative diagnosis of hypothyroidism was made. Thyroid tests and endocrinologist consultation was recommended but patient refuse it. In September 2017 dyspnea, dizziness, heaviness in the legs became worth, lack of appetite, hands and legs puffiness occurred. Appealed to Internal Medicine department of the V.N. Karazin Kharkiv National University.

Anamnesis vita is significant for uterine fibroid and thyroid hyperplasia. 2010 – Fractional uterus curettage, submucosal fibroid was removed; 2012 – hysteroscopy, polypectomy. Family history is negative for autoimmune disorders, cancer, early CVD, genetic abnormalities. Currently takes no medications, vitamin supplements or over the counter drugs.

On examination light yellowness of the skin, scleras are white. Visible mucosa is moist, of normal color. BMI 20 kg/m2. Puffy face, hands and ankles. Thyroid hyperplasia of 1^{st} degree, thyroid gland is painless to palpation. Heart borders are not expanded, sounds are muffled, rhythm regular, systolic murmur at the heart apex. HR 86 bpm. BP supine 130/90, standing 120/70. Otherwise physical examination was unremarkable.

A tentative diagnosis was made: mitral valve prolapse, 2^{nd} degree. Heart failure? Anemia?

CBC showed Hb 47 g/l, RBC $2,5\times10^{12}$/L, color index 0,56, ESR 22 mm/h, Hct 17. Blood smear: erythrocytes were mainly hypochromic, pronounced anisocytosis and poikilocytosis were present; normoblasts were not revealed, WBC morphology was within normal limits. Urinalysis: specific gravity 1016, negative for protein, glucose, ketone bodies, erythrocytes, bacteria; squamous and transitional epithelium was present in some places. Blood tests were significant for creatininemia (116,7 μmol/l) and hypokaliemia (3,0 mmol/l). GFR, estimated by Cockcroft-Gault equation showed moderate decline (46 ml/min/1,73m^2).Total protein, albumin, urea, fasting glucose, sodium and thyroid hormones were within normal ranges. ECG showed low voltage, anterior fascicular of left bundle branch block.

Thus, the hypochromic anemia was reviled and additional tests – serum iron and serum ferritin – were done. The both were decreased (iron 7,5 μmol/l, ferritin 9,45 ng/ml), which is fit with iron deficiency anemia. Uterine fibroid was thought the most likely cause. Patient was referred to gynecologist for

hospitalization and further management with the diagnosis: Iron deficiency anemia, severe degree. Uterine fibroid. Mitral valve prolapse, 2nd degree. Thyroid hyperplasia, 1st degree, euthyroid state.

Follow-up. Patient was hospitalized in the gynecological department of the regional hospital. She was given RBC transfusion and, after Hb was increased, underwent a uterus extirpation. Was discharged from the hospital with no complaints, Hb of 100 g/L, normal renal function tests and potassium level. She was advised to take oral iron and after a month her Hb was 129 g/l, RBC 4×10^{12}/L, ESR 6 mm/h.

CONCLUSIONS

The cause of our patient's condition was iron deficiency anemia (IDA). It remains a widely underdiagnosed and unappreciated women's health issue, affecting women of all ages [3–4]. Complaints presented by our patient were not specific and are typical for many diseases. Doctors can't focus only on their specialization and should look at a patient in hole, but not at «their» specialized field. None of the specialized doctors who observed our patient prescribed a CBC, thus the cause was not reviled and treatment was not effective.

Clinicians should routinely identify and treat IDA, thereby decreasing its negative impact on health and quality of life of women.

REFERENCES

1. Non-cardiovascular comorbidity, severity and prognosis in non-selected heart failure populations: A systematic review and meta-analysis / C. A. Rushton, D. K. Satchithananda, P. W. Jones, U. T. Kadam. // Int J Cardiol. – 2015. –No. 196. – P. 98–106.
2. The role of iron deficiency anemia in patients with chronic heart failure in the example of a clinical case / M. D. Nsikak-Abasi, K. I. Kornieieva, D. I. Stehnyi, M. M. Lebedinska. // The Journal of V. N. Karazin Kharkiv National University, series «Medicine». – 2017. –No. 33. – P. 86–90.
3. Iron deficiency anemia in women: a practical guide to detection, diagnosis, and treatment / [A. J. Friedman, A. Shander, S. R. Martin et al.]. // Obstet Gynecol Surv. – 2015. – No.70. – P. 342–353.
4. Camaschella C. Iron deficiency: new insights into diagnosis and treatment / C. Camaschella // Hematology Am Soc Hematol Educ Program. – 2015. –No. 2015. – P. 8–13.

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