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CONTENTS ЗМІСТ

Clinical researches

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CHANGE OF NON-SPECIFIC FACTORS OF IMMUNITY UNDER INFLUENCE OF INTERFERON INDUCTOR (CYCLOFERON) IN BRONCHIAL ASTHMA IN CHILDREN

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The aim of the work was to evaluate the effect of immunomodulation therapy on factors of nonspecific immunity in children with bronchial asthma (BA) by including interferon (cycloferon) in a standard therapy. 120 children with BA aged from 5 to 14 were examined. The main group (n = 60) included children who, in addition to basic therapy, received an interferon inducer (cycloferon) according to the generally accepted scheme. In comparison group were children who received only basic therapy (n = 60), depending on the severity of the disease. In control group were 25 healthy children. The level of serum interferon, virus-induced interferon production (VII), mitogen-stimulated production of interferon (MSI), phagocytic activity of neutrophils, as well as spontaneous and induced activity were determined. The arithmetic mean (M) and the absolute value error (m) were statistically calculated. The reliability of the differences was determined by the t-test of the Student ($p < 0,05$). The analysis of the indices of interferon status and phagocytic activity, depending on the type of therapeutic tactics, showed that as a result of the inclusion of cycloferon in the baseline, there was a significant increase in the levels of VII ($p < 0,05$) and MSI ($p < 0,05$), spontaneous and induced neutrophil activity. It was noted that this positive effect was more noticeable in moderate and severe BA ($p < 0,05$). Activation of factors of nonspecific protection contributed to a decrease in the frequency of exacerbations of BA in children, as well as a longer-term clinical remission in this contingent of children.

KEY WORDS: bronchial asthma, children, phagocytic activity, interferon inducers

ЗМІНИ НЕСПЕЦИФІЧНИХ ФАКТОРІВ ІМУНІТЕТУ ПІД ВПЛИВОМ ІНДУКТОРА ІНТЕРФЕРОНУ (ЦИКЛОФЕРОНУ) ПРИ БРОНХІАЛЬНІЙ АСТМІ У ДІТЕЙ

Чернуський В. Г., Попов М. М., Летяго Г. В., Говаленкова О. Л., Кашіна-Ярмак В. Л., Євдокимова Т. В., Гурова О. А.
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Метою роботи була оцінка впливу імуномоделюючої терапії на фактори неспецифічного імунітету у дітей з бронхіальною астмою (БА), шляхом включення до стандартної базисної схеми терапії індуктора інтерферону (циклоферону). Обстежено 120 дітей, хворих на БА, віком від 5 до 14 років. До основної групи (n = 60) увійшли діти, які до базисної терапії отримували додатково індуктор інтерферону (циклоферон) за загальноприйнятою схемою. Група порівняння – діти, які одержували тільки базисну терапію (n = 60) в залежності від ступенів тяжкості захворювання. Група контролю – 25 здорових дітей. Визначали рівень сироваткового інтерферону, вірус-індуковану продукцію інтерферону (ВІІ), мітогенстимульовану продукцію інтерферону (МСІ), фагоцитарну активність нейтрофілів, а також спонтанну і індуковану їх активність. Статистично обчислювали середню арифметичну (М), похибку абсолютної величини (m). Достовірність відмінностей визначали за t-критерієм Ст'юдента ($p < 0,05$). Аналіз показників інтерферонового статусу, а також фагоцитарної активності в залежності від виду терапевтичної тактики показав, що в результаті включення до базисної лінії терапії циклоферону відзначалося достовірне підвищення рівнів ВІІ ($p < 0,05$) і МСІ ($p < 0,05$), спонтанної і індукованої активності нейтрофілів. Відзначено, що даний позитивний ефект був більш помітний при середньому і тяжкому ступеню тяжкості БА ($p < 0,05$). Активація факторів неспецифічного захисту сприяла зменшенню частоти загострень БА у дітей, а також більш тривалій клінічній ремісії у даного контингенту дітей.

КЛЮЧОВІ СЛОВА: бронхіальна астма, діти, фагоцитарна активність, індуктори інтерферону

ИЗМЕНЕНИЕ НЕСПЕЦИФИЧЕСКИХ ФАКТОРОВ ИММУНИТЕТА ПОД ВЛИЯНИЕМ ИНДУКТОРА ИНТЕРФЕРОНА (ЦИКЛОФЕРОНА) ПРИ БРОНХИАЛЬНОЙ АСТМЕ У ДЕТЕЙ

Чернуский В. Г., Попов Н. Н., Летяго А. В., Говаленкова О. Л., Кашина-Ярмак В. Л., Евдокимова Т. В., Гуровая А. А.
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Целью работы была оценка влияния иммуномодулирующей терапии на факторы неспецифического иммунитета у детей с бронхиальной астмой (БА), путем включения в стандартную базисную схему терапии индуктора интерферона (циклоферона). Обследовано 120 детей, больных БА, в возрасте от 5 до 14 лет. В основную группу (n = 60) вошли дети, которые к базисной терапии получали дополнительно индуктор интерферона (циклоферон) по общепринятой схеме. Группа сравнения – дети, получавшие только базисную терапию (n = 60) в зависимости от степеней тяжести заболевания. Группу контроля – 25 здоровых детей. Определяли уровень сывороточного интерферона, вирус-индуцированную продукцию интерферона (ВИИ), митогенстимулированную продукцию интерферона (МСИ), фагоцитарную активность нейтрофилов, а также спонтанную и индуцированную их активность. Статистически вычисляли среднюю арифметическую (M), ошибку абсолютной величины (m). Достоверность отличий определяли по t-критерию Стьюдента ($p < 0,05$). Анализ показателей интерферонового статуса, а также фагоцитарной активности в зависимости от вида терапевтической тактики показал, что в результате включения к базисной линии терапии циклоферона отмечалось достоверное повышение уровней ВИИ ($p < 0,05$) и МСИ ($p < 0,05$), спонтанной и индуцированной активности нейтрофилов. Отмечено, что данный положительный эффект был более заметен при средней и тяжелой степени тяжести БА ($p < 0,05$). Активация факторов неспецифической защиты способствовала уменьшению частоты обострений БА у детей, а также более длительной клинической ремиссии у данного контингента детей.

КЛЮЧЕВЫЕ СЛОВА: бронхиальная астма, дети, фагоцитарная активность, индукторы интерферона

INTRODUCTION

Bronchial asthma (BA) remains one of the most urgent problems of modern pediatrics. The frequency of this pathology is growing every year and, according to WHO, about 300 million people in the world today suffer from BA. In addition, the increase in the frequency of BA is also a social problem, so this pathology steadily leads to deterioration in the quality of life of patients, the growth of disability and mortality [1–2]. Taking into account new approaches to the consideration of the mechanisms of formation of BA [1, 3–4] today proposed therapies of asthma, presented in the Global Strategy for the treatment and prevention of asthma (GINA 2009, 2011), which allow to some extent improve the patient's condition and pathology. However, these therapeutic methods show insufficient effectiveness in solving problems with multifaceted disorders in immune homeostasis and cannot cover the entire mosaic involvement of certain immunity units in the pathogenesis of BA. Therefore, despite the advances made in the diagnosis and treatment of this disease it has not been possible to obtain complete control over the course of BA [5–7].

OBJECTIVE

The aim of the study was to evaluate the effect of immunomodulation therapy on the state of nonspecific immunity in children with BA by including interferon (cycloferon) in a standard basal therapy.

MATERIALS AND METHODS

The study was carried out in the framework of the research theme of the I. I. Mechnikov Institute of Microbiology and Immunology of the National Academy of Medical Sciences of Ukraine «Investigation of immunological aspects of the course of chronic inflammatory processes of the upper respiratory tract». The study included 120 children with BA aged from 5 to 14 years with an average age of $11,6 \pm 1,5$ years. To establish the diagnosis the international classification of diseases in the 10th revision, the protocol for diagnosis and treatment of BA in children (Order of the Ministry of Health of Ukraine № 767 from 27.12.2005) and, in evaluating the therapeutic

effect of the prescribed therapy, the Global Initiative for Bronchial Asthma (GINA, 2011) were used. Three groups were identified. The main group (n = 60) included children who, in addition to basic therapy, received an interferon inducer (cycloferon) according to the scheme: 150 mg for 1, 2, 4, 6 and 8 days of therapy (№ 5) and then 150 mg after 72 hours (№ 5) (total 1500 mg). The comparison group included children who received only basic therapy (n = 60) depending on the severity of the disease. The control group comprised 25 healthy children.

The level of serum interferon, virus-induced production of interferon (VII), mitogen-stimulated production of interferon (MSI) was determined by the method of enzyme immunoassay (ELISA). The phagocytic activity of neutrophils was estimated by their ability to absorb inactivated cells of a one-day culture of staphylococci, as well as spontaneous and induced neutrophil activity from the chemiluminescence reaction by using the Bio-Orbit (Pribiri-Oy) chemiluminometer.

The study was carried out taking into account the main provisions and ethical and moral requirements of the Ukrainian Association for Bioethics and GCP (1992), GLP (2002), the principles of the Helsinki Declaration of Human Rights, the Convention of Council of Europe on Human Rights and Biomedicine.

In the statistical processing of the obtained data the arithmetic mean (M) and absolute value error (m) were calculated. To confirm the normality of the distribution for all studied indicators, the coefficient of asymmetry and kurtosis was calculated by the method of Lakin G. F. (1990). The reliability of the differences was determined by the t-test of the Student at a significance level of $p < 0,05$.

RESULTS AND DISCUSSION

In the development of BA in children the leading role belongs to immune disorders. It is known that the severity of the course and the frequency of development of asthma exacerbations in children depend on the phase, dynamism and severity of a number of specific and nonspecific systemic and local defense mechanisms. One of the most important factors protecting the respiratory tract from infectious agents is the interferon system, whose role in the pathogenesis of BA is noted by many researchers [8–11]. As a result of the study, it was found that the level of serum interferon, as well as VII and MSI in children receiving only basic therapy, were significantly lower compared to parameters in the main and control groups (table 1). Analysis of interferon status indicators depending on the type of therapeutic tactics showed, that using the GINA-recommended drugs significantly reduce levels of VII ($p < 0,05$) and MSI ($p < 0,05$). Moreover, in the heavier course of BA the weaker leukocyte synthesis of these interferons ($p < 0,05$ for all degrees of severity of the BA course) was determined. This agrees with the data of Kaidashev I. P., which show that weak elimination capacity and antiviral protection contribute to a greater probability to development of exacerbation of BA [3]. Similar results were noted in Khaitov M. R., where it was shown that the more severe the course of BA in more pronounced decrease in the level of these interferons [12] was noted.

In the main group of children who received an interferon inducer in addition to basic therapy, low values of serum interferon, VII and MSI relative to control were also noted in severe BA ($p < 0,05$), but despite this, the level of the last two indicators was still higher than in the comparison group ($p < 0,05$).

The addition of cycloferon to basic therapy for moderate BA was associated with the increase in the values of serum, MSI and VII and did not differ significantly from the control group, but they were significantly higher relative to the analogous course of BA in the comparison group ($p < 0,05$). With a mild course of BA the inclusion of cycloferon led to a slight increase in the values of the studied parameters, but this trend did not differ in the children of the comparison group.

Table 1

The content of factors of nonspecific immunity in children with BA on the background of therapy, depending on the severity, (M ± m)

Indicators	Control	Children receiving an interferon inducer and basic therapy			Children receiving an basic therapy		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Serum interferon, IU/ml	8,2 ± 3,3	8,0 ± 3,1	7,3 ± 1,5	6,4 ± 1,7*	7,6 ± 2,4	6,1 ± 2,2	4,4 ± 1,2*
VII, IU/ml	32,0 ± 7,8	31,6 ± 6,5	28,1 ± 4,8	17,6 ± 3,5*	22,3 ± 4,8*	16,4 ± 3,5*#	9,1 ± 1,6*#
MSI, IU/ml	38,0 ± 9,6	36,7 ± 6,4	25,6 ± 4,7*	19,7 ± 3,5*	24,8 ± 5,8*	16,7 ± 6,2*#	6,5 ± 1,8*#
Phagocytic activity of neutrophils, %	58,0 ± 6,8	57,6 ± 5,7	49,5 ± 6,3	25,7 ± 5,3*	54,8 ± 6,1	32,5 ± 4,4*#	10,3 ± 2,9*#
Spontaneous activity of neutrophils, c. u.	2,6 ± 0,80	2,5 ± 0,40	1,8 ± 0,50	1,6 ± 0,20*	2,5 ± 0,40	1,9 ± 0,30	1,4 ± 0,4*
Induced neutrophil activity, c. u.	29,7 ± 8,20	28,8 ± 6,1	24,3 ± 4,8	16,5 ± 4,2*	28,3 ± 7,1	19,6 ± 4,8*#	11,3 ± 2,8*

*Notes: * p < 0,05 - the differences between the indicators of the first and second comparison groups in comparison with the control group; # P < 0,05 - differences of the studied parameters with average and severe degrees of severity of the BA of the main group and the comparison group.*

The role of neutrophils in the course of BA and, especially in the process of development of exacerbation, is emphasized by a number of researchers [4, 13]. According to our data, the phagocytic activity of neutrophils directly depended on the severity of the course of BA and was several times lower in severe than in control and mild course ($p < 0,05$). This trend was especially noticeable in the children of the comparison group who received only basic therapy, including glucocrticosteroids. In the main group of children, the neutrophil activity indicators were close to the control group and even in the severe case the phagocyte (25,7 ± 5,3 vs 10,3 ± 2,9, $p < 0,05$) and induced (16,5 ± 4,2 vs 11,3 ± 2,8, $p < 0,05$) activity were significantly higher, which is related to the immunomodulatory property of cycloferon. The positive effect of interferon preparations is also indicated in a number of scientific works, which notes that when choosing a therapeutic approach for the treatment of BA, it is necessary to take into account the level of production of interferons with the addition of immunomodulatory therapy, in particular interferon preparations [8, 14]. Researchers note that interferon therapy is a promising direction in the complex treatment of virus-induced BA in the remission stage as one of the measures of secondary prevention of the disease, and can also be used for primary prevention of BA in children from high-risk groups of its formation. However, it should be noted that the practical application of interferon inducers both in monotherapy and in combined therapy of BA in children has advantages over the use of interferon preparations, since the synthesis of interferons when administered inducers of interferon genesis is regulated by the body itself, which prevents possible side reactions.

CONCLUSIONS

Thus, the study showed that an important aspect of increasing the effectiveness of baseline therapy of BA, proposed by GINA (2009, 2011), is the additional inclusion of inducers of interferon, in particular, cycloferon. This drug contributed to the enhancement of phagocytic activity of neutrophils, and also led to an increase in leukocyte synthesis of VII and MSI, which was particularly noticeable in moderate and severe course of BA. Considering the fact that in the exacerbation of BA the huge importance is given to infectious agents, the intensification of the activity of factors of non-specific immunity in the future will contribute to an increase in antimicrobial protection of the body, and consequently, to a decrease in relapses of asthma in children, as well as to a prolonged clinical remission in this contingent of children.

PROSPECTS FOR FUTURE STUDIES

Take into account the positive effect of the interferon inducer (cycloferon) on nonspecific defense factors, it is promising to continue the study in the direction of assessing its effect on the humoral and cellular link of immunity in children with BA.

REFERENCES

1. Balabolkin I. I. Bronkhial'naya astma u detey / I. I. Balabolkin, V. A. Bulgakova. – Moskva : MIA, 2015. – 144 s.
2. Geppe N. A. Aktual'nost' problemy bronkhial'noy astmy u detey / N. A. Geppe // Pediatriya. – 2012. – T. 91, № 3. – S. 76–82.
3. Kaydashev I. P. T-kletochnaya regulyatsiya pri atopicheskikh zabolevaniyakh / I. P. Kaydashev // Klinicheskaya immunologiya. Allergologiya. Infektologiya. – 2011. – № 9. – S. 18–21.
4. Okhotnikova Ye. N. Patogeneticheskiye osobennosti bronkhoobstruktivnogo sindroma u detey i sovremennyye vozmozhnosti neotlozhnoy terapii / Ye. N. Okhotnikova // Astma i allergiya. – 2013. – № 2. – S. 52–61.
5. Okhotnikova Ye. N. Bronkhial'naya astma u detey rannego vozrasta: osobennosti lecheniya / Ye. N. Okhotnikova // Klinicheskaya immunologiya, allergologiya, infektologiya. – 2014. – № 4. – S. 5–11.
6. Chernysheva O. Ye. Sovremennyye predstavleniya o patogeneze bronkhial'noy astme u detey / O. Ye. Chernysheva // Zdorov'ye rebenka. – 2014. – № 5. – S. 84–90.
7. Papadopoulos N. G. International consensus on (ICON) pediatric asthma / N. G. Papadopoulos [et al.] // Allergy. – 2012. – Vol. 67. – P. 976–997.
8. Zaytseva O. V. Virusindutsirovannaya bronkhial'naya astma u detey: znacheniye sistemy interferona / O. V. Zaytseva, E. E. Lokshina, S. V. Zatseva // Pediatriya. Zhurnal im. G.N. Speranskogo. – 2017. – № 2. – S. 99–105.
9. Bergauer A. IFN-α/IFN-λ responses to respiratory viruses in paediatric asthma / A. Bergauer, N. Sopel, B. Krob // Eur Respir J. – 2017. – № 49. – P. 96–110.
10. Koch S. Role of Interferon-γ in Allergic Asthma / S. Koch, S. Finotto // J. Innate Immun. – 2015. – № 7. – P. 224–230.
11. Lambrecht N. B. The immunology of asthma / N. B. Lambrecht, H. Hammad // Nature Immunology. – 2015. – № 16. – P. 45–56.
12. Khaitov M. R. Respiratory virus induction of alpha-, beta- and lambda-interferons in bronchial epithelial cells and peripheral blood mononuclear cells / M. R. Khaitov, V. Laza-Stanca, M. R. Edwards // Allergy. – 2009. – Vol. 64, issue 3. – P. 375–386.
13. Anisimova N. YU. Fenotip i fagotsitarnaya aktivnost' neytrofilov krovi bol'nykh bronkhial'noy astmoy v periode obostreniya / N. YU. Anisimova // Immunologiya. – 2012. – № 6. – S. 318–322.
14. Macharadze D. SH. Virusy i astma: bol'she voprosov, chem otvetov / D. SH. Macharadze // Lechashchiy vrach. – 2009. – № 10. – S. 69–76.

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CHANGING OF THE DOSE COEFFICIENT OF THE MAJOR GROUPS OF DRUGS FOR PATIENTS WITH IMPLANTED PACEMAKERS, DEPENDING ON THE STAGE OF HYPERTENSION

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We observed 131 patients (70 men and 61 women) aged 69,5 ± 11,6 at the annual stage of drug therapy after implantation of pacemakers in the DDD / DDDR modes, VVI / VVIR and CRT-P / CRT-D. Patients were divided into 2 groups – I and II stage of AH. . In each group, the dose rate was defined in major groups of cardiac drugs at every stage of research. The results showed that the dose coefficient of the major groups of cardiac drugs in patients with pacemaker and AH was determined by the stage of AH, what is more AH stage III required higher doses of diuretics and anti-arrhythmic drugs than AH stage II during the hole period of observation. Patients with implanted pacemaker and AH require more careful titration of the major groups of cardiac drugs, taking into account the stage of AH.

KEY WORDS: pacing, the stage of hypertension, the dose rate

ЗМІНА КОЕФІЦІЄНТА ДОЗИ ОСНОВНИХ ГРУП МЕДИЧНИХ ПРЕПАРАТІВ У ПАЦІЄНТІВ З ІМПЛАНТОВАННИМИ ЕЛЕКТРОКАРДІОСТИМУЛЯТОРАМИ В ЗАЛЕЖНОСТІ ВІД СТАДІЇ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

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Спостерігали 131 пацієнта (70 чоловіків і 61 жінку) у віці 69,5 ± 11,6 на річному етапі підтримуючої медикаментозної терапії після імплантації електрокардіостимуляторів (ЕКС) в режимах DDD / DDDR, VVI / VVIR і CRT-P / CRT-D. Пацієнти були розділені на 2 групи – I та II стадії АГ. У кожній групі визначався коефіцієнт дози основних груп кардіологічних препаратів на кожному з етапів дослідження. Результати показали, що коефіцієнт дози основних груп кардіологічних препаратів у пацієнтів з ЕКС і АГ визначався стадією АГ, причому на всьому періоді спостереження АГ III стадії вимагала більш високих доз призначення діуретиків та анти аритмічних препаратів, ніж АГ II стадії. Пацієнти з імплантованими ЕКС і АГ вимагають більш ретельного титрування основних груп кардіологічних препаратів з урахуванням стадії АГ.

КЛЮЧОВІ СЛОВА: електрокардіостимуляція, стадія артеріальної гіпертензії, коефіцієнт дози

ИЗМЕНЕНИЕ КОЭФФИЦИЕНТА ДОЗЫ ОСНОВНЫХ ГРУПП МЕДИКАМЕНТОЗНЫХ ПРЕПАРАТОВ У ПАЦИЕНТОВ С ИМПЛАНТИРОВАННЫМИ ЭЛЕКТРОКАРДИОСТИМУЛЯТОРАМИ В ЗАВИСИМОСТИ ОТ СТАДИИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Наблюдали 131 пациента (70 мужчин и 61 женщину) в возрасте 69,5 ± 11,6 на годовом этапе поддерживающей медикаментозной терапии после имплантации электрокардиостимуляторов (ЭКС) в режимах DDD/DDDR, VVI/VVIR и CRT-P/CRT-D. Пациенты были разделены на 2 группы – I и II стадии АГ. В каждой группе определялся коэффициент дозы основных групп кардиологических

препаратов на каждом из этапов исследования. Результаты показали, что коэффициент дозы основных групп кардиологических препаратов у пациентов с ЭКС и АГ определялся стадией АГ, причем на всем периоде наблюдения АГ III стадии требовала более высоких доз назначения диуретиков и антиаритмических препаратов, чем АГ II стадии. Пациенты с имплантированными ЭКС и АГ требуют более тщательного титрования основных групп кардиологических препаратов с учетом стадии АГ.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимуляция, стадия артериальной гипертензии, коэффициент дозы

INTRODUCTION

Permanent cardiac pacemaker is the leading method for treatment patients with significant bradyarrhythmias, improving survival and quality of life [1–2], however, always requires the modification of concomitant drug therapy [3]. Despite this, the change in the dose of the main groups of cardiac drugs in patients with pacemakers, depending on the stage of arterial hypertension (AH), has not been studied.

OBJECTIVE

The aim of the study was to evaluate the change in the dose of the main groups of cardiac drugs in patients with cardiac pacemaker at the annual stage of observation, depending on the stage of AH.

MATERIALS AND METHODS

131 patients (70 men and 61 women) aged 69,5 ± 11,6 years who underwent permanent pacing were examined in the department of ultrasound and clinical instrumental diagnosis and minimally invasive interventions SI «V. T. Zaytsev Institute of General and Emergency Surgery NAMS of Ukraine». The II stage of AH was diagnosed in 92 patients, 39 – had the III stage of AH according to the recommendations of the Association of Cardiologists of Ukraine [4]. The indications for pacemaker implantation were atrio-ventricular block(AV) – 87 people(62 %), permanent atrial fibrillation(AF) – 19 people (14 %) and sick sinus node syndrome(SSS) – 34 people (24 %) with pacing modes DDD/DDDR and VVI /VVIR and dilated cardiomyopathy (DCM) – 2 people (2 %) with cardiac resynchronization therapy (CRT-P and CRT-D).

Patients aged less than 40 years, presence of concomitant stable angina IV functional class (FC), chronic heart failure (CHF) IV FC and/or stage III, the stimulation of the right ventricle (RV) and/or left ventricular (LV) less than 50 % were excluded from the study.

Drug therapy before the implantation, in the early postimplantation period (3–5 days), after 6 months and 1 year after depending on the stage of AH was represented by the following groups of drugs: C03 diuretics (furosemide, torasemide, hydrochlorothiazide); C07A betaadrenergetic blockers (carvedilol, metoprolol, bisoprolol, nebivolol); C08C A calcium channel antagonists (dihydropyridine derivatives – amlodipine, nifedipine and fenilalkilamin derivatives – verapamil); C09A angiotensin converting enzyme (ACE) inhibitors (enalapril, lisinopril, ramipril); C09C angiotensin II receptor blockers (ARBs) (losartan, candesartan). Apart from this were used: B01A A anticoagulants (warfarin); B01A C antiplatelet therapy (aspirin, clopidogrel); B01A E direct thrombin inhibitors (dabigatran etexilate), and V01A F direct factor Xa inhibitors (rivaroxaban) (new anticoagulants); C01B D01 amiodarone; C01A A hydroxymethylglutaryl inhibitors (HMG) coenzyme A (CoA) (statins) (atorvastatin, simvastatin).

Dose coefficient for each group of drugs has been calculated as the average value among the ratios of each drug dose group versus middle therapeutically for this drug, taken as 1.0. It corresponds to the group of anticoagulants warfarin 5 mg; antiplatelet agents – 75 mg of aspirin and 75 mg clopidogrel; 75 mg of dabigatran etexilate and 5 mg rivaroxaban; 200 mg amiodarone; 10 mg ivabradine; in the group of diuretics – 40 mg furosemide, 5 mg torasemide, 12.5 mg hydrochlorothiazide, 2.5 mg indapamide; in the group of beta-adrenergic blockers – 5 mg bisoprolol, 100 mg metoprolol, 12,5 mg carvedilol, 5 mg nebivolol, 5 mg betaxolol, 50 mg atenolol; in the group of calcium channel antagonists – amlodipine 10 mg, nifedipine 90 mg, verapamil 80 mg; in the group of ACE inhibitors – 10 mg enalapril, 10 mg of lisinopril, 5 mg ramipril, 10 mg fosinopril; group ARBs – 50 mg losartan, 8 mg candesartan; in the group of statins – 20 mg

atorvastatin, 20 mg simvastatin, 10 mg rosuvastatin.

Patients were divided into 2 groups – II and III stage AH. In each group, the dose coefficient for each group of drugs was determined at each stage of the study.

The results obtained are processed after forming the database. Statistical evaluation was performed using Microsoft Excel (for parametric data: M – mean value, sd – standard deviation; for nonparametric data: absolute (n, the number) and relative (p, %) of the unit). The probability of differences between groups was determined using a nonparametric U – Mann-Whitney test. The expected result was determined by level of reliability $p < 0,05$ and $p < 0,01$.

RESULTS AND DISCUSSION

The results of the study of the dose coefficient of prescribing antihypertensive drugs in patients with cardiac pacemaker at the annual stage of observation, depending on the stage of AH are presented in tab. 1.

Table 1

The dose coefficient of prescribing antihypertensive drugs in patients at the annual stage of observation after implantation of cardiac pacemaker, depending on the stage of AH (M ± sd, %)

Drug	Stage of AH							
	II stage				III stage			
	Before implantation	3-5 after	6 month.	1 year	Before implantation	3-5 after	6 month.	1 year
C 03A Diuretics	0,9 ± 0,1	1,1 ± 0,3	1 ± 0,2	1 ± 0,2	1,1 ± 0,8	1,3 ± 0,8	1,2 ± 0,8	1,2 ± 0,8
C07A BAB	0,8 ± 0,4*	0,9 ± 0,3^	0,8 ± 0,3	0,8 ± 0,3	0,9 ± 0,2*	0,9 ± 0,2^	0,9 ± 0,3	0,8 ± 0,4
C08 CA Ca-channel antagonists	0,9 ± 0,1	0,8 ± 0,1	0,9 ± 0,2	0,9 ± 0,2**	1 ±	0,9 ± 0,1	0,9 ± 0,2	0,8 ± 0,2**
C 09A ACE-inhibitor	1 ± 0,1	0,9 ± 0,2^	0,8 ± 0,2	0,8 ± ,2	1 ± 0,2	0,9 ± 0,1^	0,8 ± 0,2	0,8 ± 0,2
C09 C ARBs II	1 ± 0	1 ± 0	1 ± 0	1 ± 0	0	0	1 ± 0	1 ± 0

*Note: * p < 0.05 - between values in the group of AH before the implantation of pacemaker; ^p < 0.05 – between values in the group of AH in the acute period after the implantation of pacemaker; ** P < 0.05 – between values in the group of AH in 1 year after the implantation of pacemaker.*

Initially, the dose coefficient of diuretics was determined by the stage of AH and was higher in the stage III of AH. With the implantation of pacemaker in the early postoperative period, it increased further subsequently decreased in both groups, however, exceeding the initial level.

Before the implantation of pacemaker, the dose coefficient of β-blockers was higher in the group of AH stage III. After the implantation of pacemaker in the early postoperative period, the dosage increased in the II stage of AH, at an annual stage it decreased in both groups.

Initially, the dose coefficient of Ca antagonists was higher in the group stage III of AH. With the implantation of pacemaker in the early postoperative period, the dosage was reduced in both groups, however, by the annual period in the group stage II of AH, it returned to the initial doses. In stage III of AH, the dosage was reduced at all stages of the observation.

Initially the same dose coefficient of ACE inhibitors with implantation of cardiac pacemaker consistently decreased at all stages of observation in both groups.

Before the implantation of cardiac pacemaker, the dose coefficient of ARBs II was higher in the group stage II of AH and remained an average therapeutic at all stages of observation. With stage III of AH, the dosage was increased by the annual stage of observation.

The results of the study of the dose coefficient of prescribing main groups of cardiac drugs in patients with cardiac pacemaker at the annual stage of observation, depending on the stage of AH are presented in tab. 2.

Table 2

The dose coefficient of prescribing main groups of cardiac drugs in patients at the annual stage of observation after implantation of cardiac pacemaker, depending on the stage of AH (M ± sd, %)

Drug	Stage of AH							
	II stage				III stage			
	Before the implantation	3-5 after	6 month.	1 year	Before the implantation	3-5 after	6 month.	1 year
B 01A A Anticoagulant	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
B 01A C Antiplatelet	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
C 01B Antiarrhythmic	1,5 ± 0,5	1,6 ± 0,5	1,3 ± 0,9*	1,1 ± 0,9**	1,6 ± 0,7	1,8 ± 0,8	1,2 ± 0,7*	1,2 ± 0,7**
C01A A Statins	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0

*Note: *p < 0.05 - between values in the group of AH in 6 months after implantation of the pacemaker; ** P < 0.05 - between values in the group of AH in 1 year after implantation of the pacemaker.*

Initially, the dose coefficient of antiplatelet agents, anticoagulants and statins was the same in both groups and did not change at all stages of the observation.

Before the implantation of cardiac pacemaker, the dose coefficient of antiarrhythmic drugs was higher in the group stage III of AH. With the implantation of pacemaker, the dosage increased in the early postoperative period and then gradually decreased by the annual period in both groups.

This study showed that implantation of cardiac pacemaker in patients with AH requires an increase in the dose of diuretics, β-blockers and antiarrhythmic drugs in the early postoperative period, which corresponds to the data [5–7].

The dose coefficient of the main groups of cardiac drugs in patients with ECS and AH was determined by the stage of AH, besides, at the annual stage of follow-up AH III stage required higher doses of diuretics and antiarrhythmic drugs than in the group stage II of AH, the data are new and have not been confirmed in the literature.

CONCLUSIONS

1. The dose coefficient of the major groups of cardiac drugs in patients with pacemaker and AH was determined by the stage of AH, what is more AH stage III required higher doses of diuretics and anti-arrhythmic drugs than AH stage II during the hole period of observation.

2. Patients with implanted pacemaker and AH require more careful titration of the major groups of cardiac drugs, taking into account the stage of AH.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study drug optimization in patients with AH and cardiac pacing in a period of more than one year with correction of the frequency and doses of the main groups of cardiac drugs.

REFERENCES

1. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation / [R. Coma Samartín, F. Ruiz Mateas, M. Fidalgo Andrés et al.]. // Rev Esp Cardiol (Engl Ed). – 2013. – № 66 (12). – P. 72–959.
2. Leadless Cardiac Pacemakers: Back to the Future. / M.Miller, P. Neuzil, S. Dukkipati, V. Reddy. // J Am Coll Cardiol. – 2015. – № 66 (10). – P. 89–1179.
3. Shanina I. V. Frequency of detached cardiac drugs prescribing in patients of different classes QRS complex duration on the permanent pacing background/ I. V. Shanina, D. E. Volkov// The Journal of V. N. Karazin Kharkiv National University, series «Medicine» – 2014. – № 27. – P.33–37.
4. Recommendations of Ukrainian Association of Cardiology on prevention and treatment of hypertension. Guide to the National Programme for prevention and treatment of hypertension, 2008. – 80 p. – (VMB K.: PP). – (4).
5. Shanina I. V. Frequency of detached cardiac drugs prescribing in patients of different classes QRS complex duration on the permanent pacing background/ I. V. Shanina, D. E. Volkov // The Journal of V. N. Karazin Kharkiv National University, series «Medicine» – 2014. – № 27. – P. 33–37.
6. Kolomytseva I.N. Functional class of chronic heart failure and supportive drug therapy in patients at the annual stage pacing / I.N. Kolomytseva // Canadian Journal of Education and Engineering. – 2015. – № 2 (12). – P. 569–578.
7. Atrial-based pacing has no benefit over ventricular pacing in preventing atrial arrhythmias in adults with congenital heart disease. / [P. Opic, S. Yap, M. Van Kranenburg et.al.]. // Europace. – 2013. – № 15 (12). – P. 62–1757.

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HEART RATE VARIABILITY PARAMETERS IN PATIENTS WITH ARTERIAL HYPERTENSION IN DEPENDENCE ON THE TYPE OF DAILY BLOOD PRESSURE PROFILE

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Violation of functioning of the autonomic nervous system is an important factor in the formation and progression of arterial hypertension (AH). Abnormal nocturnal blood pressure (BP) reduction is regarded as an independent prognostic factor for cardiovascular complications in patients with AH. One of the possible factors that determine the violation of BP circadian rhythm can be imbalance of different parts of autonomic nervous system.

The aim of our study was to study heart rate variability (HRV) in patients with AH, dependently of BP profile. 72 patients with AH were examined. Average age was 57 ± 11 years.

All patients underwent ambulatory BP (ABPM) and ECG monitoring. To define the daily profile the nocturnal BP dip was quantified and for HRV evaluation the frequency analysis method was used. HRV changes in patients with AH present with reduced total power and with a violation in the ratio of the powers of very low, low and high frequencies, enhanced sympathycotension and influence of humoral factors. Violations of systolic BP (SBP) daily profile was mainly characterized by an increase in the power of low frequency waves, which indicates an intensification of sympathetic and decreased parasympathetic influences. Violations of diastolic BP (DBP) daily profile were mainly characterized by a relative increase in the power of very low frequency waves. The obtained results showed that in the management of patients with AH it is important not only to control the circadian SBP and DBP profiles, but the evaluation of HRV also.

KEY WORDS: heart rate variability, arterial hypertension, ambulatory blood pressure monitoring, circadian blood pressure profile

ПОКАЗНИКИ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ПАЦІЄНТІВ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ЗАЛЕЖНО ВІД ТИПУ ДОБОВОГО ПРОФІЛЮ АРТЕРІАЛЬНОГО ТИСКУ

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Порушення функціонування вегетативної нервової системи є важливим фактором у формуванні та прогресуванні гіпертонічної хвороби (ГХ). Недостатнє або надмірне нічне зниження артеріального тиску (АТ) розглядається як незалежний прогностичний фактор серцево-судинних ускладнень у пацієнтів з ГХ. Одним з можливих чинників, які визначають порушення циркадного ритму АТ може бути дисбаланс вегетативної нервової системи. Ціллю нашого дослідження було вивчення особливостей показників варіабельності серцевого ритму (ВСР) у пацієнтів з ГХ. Обстежено 72 пацієнта з гіпертонічною хворобою. Середній вік 57 ± 11 років. Всім пацієнтам проводилося добове моніторування АТ і ЕКГ. Для визначення добових профілів систолічного АТ (САТ) та діастолічного АТ (ДАТ) розраховували ступінь нічного зниження АТ. Для оцінки ВСР використовувалися методи частотного аналізу. Зміни показників ВСР у пацієнтів з ГБ полягають у зниженні загальної потужності спектра з порушеннями в співвідношеннях потужностей дуже низьких, низьких та високих частот, посиленні симпатикотонии та впливу гуморальних факторів. Результати показали, що порушення добового профілю САД при зниженні загальної потужності спектра в основному характеризуються збільшенням потужності низьких частот ВСР, що свідчить про посилення симпатичних та зниження парасимпатичних впливів, а добового профілю ДАТ – у відносному збільшенні потужності дуже низьких частот ВСР, що свідчить про посилення гуморальних впливів. Результати показують важливість в діагностиці та контролі ГБ добових профілів не тільки САД, але і ДАТ, доповнюючи їх оцінкою показників ВСР.

КЛЮЧОВІ СЛОВА: варіабельність серцевого ритму, гіпертонічна хвороба, добове моніторування артеріального тиску, добовий профіль артеріального тиску

ПОКАЗАТЕЛИ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА У ПАЦИЕНТОВ С ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ В ЗАВИСИМОСТИ ОТ ТИПА СУТОЧНОГО ПРОФИЛЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ

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Нарушение функционирования вегетативной нервной системы является важным фактором в формировании и прогрессировании гипертонической болезни (ГБ). Недостаточное или избыточное ночное снижение артериального давления (АД) рассматривается как независимый прогностический фактор сердечно-сосудистых осложнений у пациентов с ГБ. Одним из возможных факторов, которые определяют нарушение циркадного ритма АД, может быть дисбаланс вегетативной нервной системы. Целью нашего исследования было изучить особенности показателей вариабельности сердечного ритма (ВСР) у пациентов с ГБ. Обследовано 72 пациента с гипертонической болезнью. Средний возраст 57 ± 11 лет. Всем пациентам проводилось суточное мониторирование АД и ЭКГ. Для определения суточных профилей систолического АД (САД) и диастолического АД (ДАД) рассчитывали степень ночного снижения АД. Для оценки ВСР использовались методы частотного анализа. Изменения показателей ВСР у пациентов с ГБ состоят в снижении общей мощности спектра с нарушениями в соотношениях мощностей очень низких, низких и высоких частот, усиления симпатикотонии и усилении влияния гуморальных факторов. Результаты показали, что нарушения суточного профиля САД при снижении общей мощности спектра в основном характеризуются увеличением мощности низких частот ВСР, что свидетельствует об усилении симпатических и снижении парасимпатических влияний, и суточного профиля ДАД – в относительном увеличении мощности очень низких частот ВСР, что свидетельствует об усилении гуморальных влияний. Результаты показывают важность учитывания в диагностике и контроле ГБ суточных профилей не только САД, но и ДАД, дополняя их оценкой показателей ВСР.

КЛЮЧЕВЫЕ СЛОВА: вариабельность сердечного ритма, гипертоническая болезнь, суточное мониторирование артериального давления, суточный профиль артериального давления

INTRODUCTION

Arterial hypertension (AH) remains one of the most worldwide health and social problem due to its high prevalence, high risk of complications and the lack of adequate blood pressure (BP) control [1].

Autonomic dysfunction, along with heredity and endocrine-metabolic imbalance is an important factor in the formation and progression of the AH. Therefore, the study of autonomic regulation may be the key to understanding the clinical and pathogenetic features of hypertension.

At the present time to assess the state of the autonomic nervous system (ANS) is widely used study of heart rate variability (HRV) [2–3]. Studies in this area showed greater sympathetic drive in the early stages of AH, reduced HRV and increase very low frequency effects on the heart rhythm with the progression of the disease [4–5].

In accordance with the results of recent studies lack of adequate physiological nocturnal BP reduction or excessive BP lowering at night regarded as an independent prognostic factor for cardiovascular complications in patients with hypertension. One of the possible factors that determine the violation of BP circadian rhythm can be imbalance of different parts of autonomic nervous system.

OBJECTIVE

To study HRV particular qualities in patients with AH, dependently of BP profile.

MATERIALS AND METHODS

72 patients with AH were examined. The study involved 28 men (39 %) and 44 women (61 %). Average age was 57 ± 11 years.

AH of stage I was diagnosed in 15 % of patients, stage II – in 67 %, stage III – 18 %. AH of 1 grade was determined in 36 % of patients, grade 2 – 22 %, grade 3 – 14 %. Heart failure (HF) was diagnosed in 72% cases: HF stage I - 39%, HF stage IIA – 33 %, I functional class (FC) of HF was determined in 22 % of patients, II FC – 42 %, III FC – 8 %; coronary heart disease (CHD) – 76 % of cases: stable angina (I–III FC) – 27 %, postinfarction cardiosclerosis (PICS) – 3 %.

Exclusion criteria were secondary hypertension, hemodynamically significant valvular heart disease, cardiomyopathy of any

genesis, heart failure stage III, FC IV by NYHA, any acute condition (infection, trauma, surgery) within the previous 3 months, chronic diseases in stage of decompensation or exacerbation, cancer, as well as any circumstances that hinder the conduction of ABPM or Holter ECG monitoring.

All patients underwent ABPM and Holter ECG monitoring using a computer system «Kardiosens» (HAI Medica, Ukraine) with the oscillometric method of blood pressure measurement.

The monitoring was performed in the conditions of patient normal working day, the cuff was placed at the non-dominant arm using an appropriately sized cuff. According to Ambulatory Blood Pressure Monitoring International Recommendations 2013 [6], blood pressure was measured every 15 minutes during the day and 30 minutes at night. Daytime and night-time periods were defined based on a diary, in which participants were asked to record their activities and sleep times during the monitoring session. Editing ABPM, in accordance Ambulatory Blood Pressure Monitoring International Recommendations [6] if any value outside preset limits (see below) was detected during a recording, that measurement was rejected:

– Systolic blood pressure (SBP) > 250 or < 70 mm Hg,

– Diastolic blood pressure (DBP)> 150 or < 40 mm Hg,

– Pulse pressure (PP) > 150 or < 20 mm Hg,

– Heart rate (HR)> 200 or < 20 per minute.

Also ABPM data series were considered invalid for analysis in the following cases:

– Absence of ≥ 30 % of the scheduled measurements,

– Lack of data for > 2 consecutive hourly intervals,

– If patient maintained an irregular rest-activity schedule during consecutive 24-h periods of monitoring,

– If the nighttime sleep span was < 6 h or > 12 h [6].

To define the daily profile the nocturnal BP dip was quantified as the relative decline in mean BP from awake (daytime) to asleep (night-time) periods, and was calculated for SBP, DBP and PP separately using the following equation: ((mean awake BP – mean asleep BP) / mean awake BP) × 100 %. Depending on the value of this ration the following types of daily BP profile were defined: «dipper» – physiological decrease in BP during the night – sleep-time relative BP decline 10–20 %; «over dipper» – an excessive fall in BP at night, sleep-time relative BP decline > 20 %; «non dipper» – 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 [6].

HRV evaluation was carried out after exclusion of artifacts and arrhythmias. From the daily ECG record, 5-minute intervals were allocated, in the morning, during rest period, according to the patient diary. Frequency analysis method was used, and included the following parameters: total power (TP), low frequency (LF) (0.04–0.15 Hz), very low frequency (VLF) (0.003–0.04 Hz) and high frequency (HF) (0.15–0.4 Hz) components, the ratio LF/HF (index of the sympathovagal balance) [7]. Patients were divided into 4 groups according to the type of daily SBP profile and 4 groups – according to the type of daily DBP profile. For each group mean (M) and standard deviation (sd) were calculated. HRV parameters were compared in patients with pathological types of BP daily profile o – non dipper, night-picker and over dipper – with the physiological type – dipper – in accordance with the selected ABPM index, as well as in pairs in the groups of SBP and DBP profiles, and in healthy subjects. Software Statistical Package for Social Sciences (SPSS) was used for data analysis. For variables with asymmetric distribution in addition to M and sd median (Me) and 25^{th} and 74^{th} percentiles were reported. Statistical significance of the differences between the obtained results and recommended standards was calculated based on the t-test for the case of 2 different samples with known standard deviations (TP, HF, LF) and for the known population mean (LF/HF). Student's t-test was reported for variables having normal distribution (LF/HF), whereas Mann-Whitney's U-test was reported for variables having asymmetric distribution (TP, HF, LF, VLF).

RESULTS AND DISCUSSION

SBP profile of «dipper» type was set in 39 % of patients, «non dipper» – 43 %, «night-piker» – 10 %, «over dipper» – 8 %. DBP daily profile of «dipper» type was defined in 36 % of cases, «non dipper» – 29 %, «night-piker» – 4 %, «over dipper» – 31 %.

The total power of the HRV (TP) was lower than the recommended values in all groups of BP profile, except the group of non-dippers, in

which TP slightly exceeded the normal values in both subgroups – SBP-non-dipper and DBP-non-dipper (Table). Statistically significant differences were found in comparison with the recommended standards in all investigated HRV domains. In all BP daily profile subgroups, the power of the high-frequency and low-frequency components were significantly lower than the normal values. The lowest values of HF and LF were observed in the group of SBP-night-pickers (Table). VLF values in all groups were higher than normal, in subgroups of SBP-dippers, SBP- and DBP-non dippers, DBP-over dippers these differences were statistically significant at the level of $p < 0.05$ (Table). The index of the sympathovagal balance exceeded the recommended standards also. Differences were found to be statistically significant in all groups, except for DBP-night-pickers and DBP-over diapers (Table).

Table

HRV parameters in patients with AH dependently of BP daily profile, M ± sd

		TP	***HF***	***LF***	***VLF***	***LF/ HF***
SBP	dipper	2612 ± 3728	118 ± 140*	448 ± 480*	1145 ± 1104*	4,47 ± 2,31*
	non dipper	3794±3244	300±476*	684±788*	1551±1501*	3,19±1,68*
	night-picker	2110±2436	92±61*	356±330*	950±1130	3,5±1,38*
	over dipper	2560±2466	292±383*	448±321*	864±575	3,56±2,26*
DBP	dipper	3240±4201	212±344*	612±772*	1263±11774	3,52±1,45*
	non dipper	3724±3300	277±479*	579±660*	1540±1644*	3,48±1,82*
	night-picker	2508±1619	147±73*	432±286*	1036±618	3,03±2,05
	over dipper	2396±2127	161±231*	443±368*	1092±985*	4,3±2,73
recommended standards		3466 ± 1018	975 ± 203	1170 ± 416	765± 410	1.5 – 2.0

When comparing HRV parameters in pairs in the subgroups of BP daily profile types there were no statistically significant differences in TP. When comparing the physiological type of BP daily profile – dipper – with pathological ones, the TP in the subgroup of SBP-non dippers was statistically significantly higher than that in the subgroup of SBP-dippers (Figure 1).

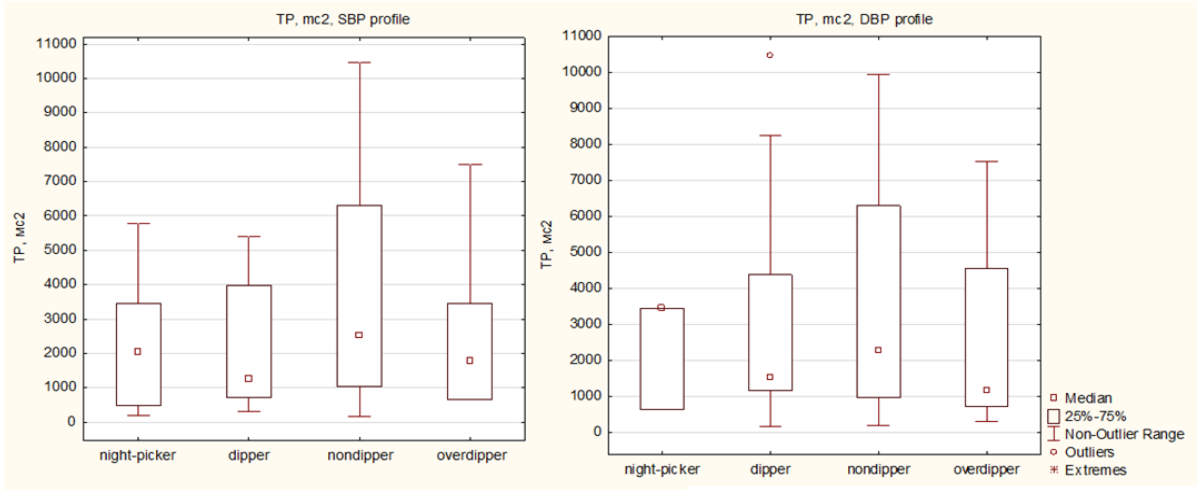

Fig. 1. The total power (TP) of the HRV, depending on the type of daily profiles of SBP and DBP

When comparing HF in pairs in subgroups of BP daily profile types, no significant differences were found. When comparing the pathological types of BP daily profile with the dipper type in the groups of non-dippers and over dippers a greater degree of scattering was noted, and the HF value in the subgroup of SBP-non dippers was significantly higher than that in the subgroup of SBP-dippers at a level of $p < 0.05$ (Fig. 2).

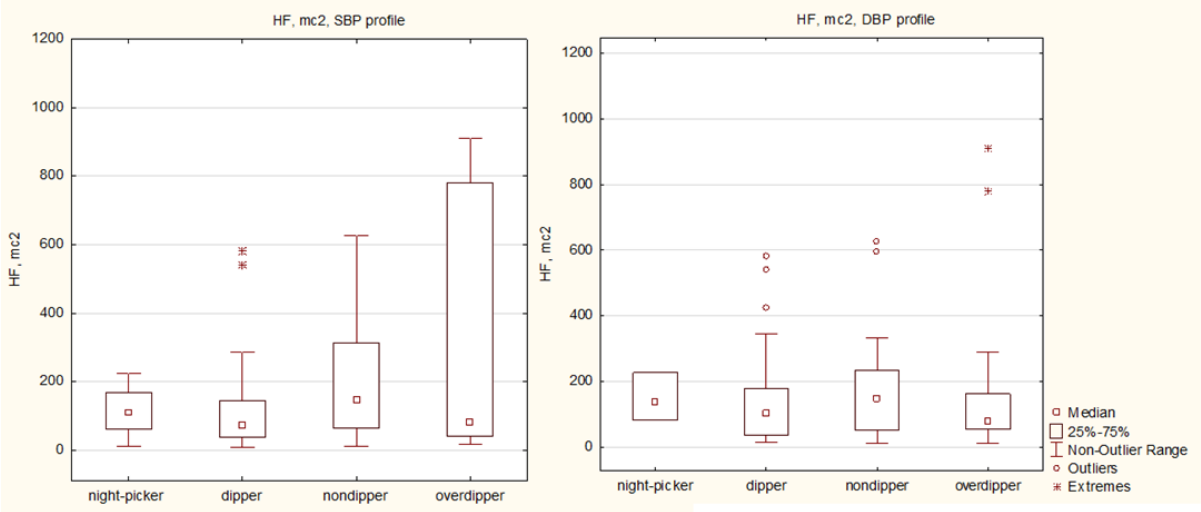

Fig. 2. The high-frequency component (HF) of the HRV, depending on the type of daily profiles of SBP and DBP

When comparing the powers of LF and VLF in pairs in the subgroups of BP daily profile types, and comparing the values of these parameters of pathological types of BP daily profile with the type dipper, no significant differences were found (Fig. 3, 4).

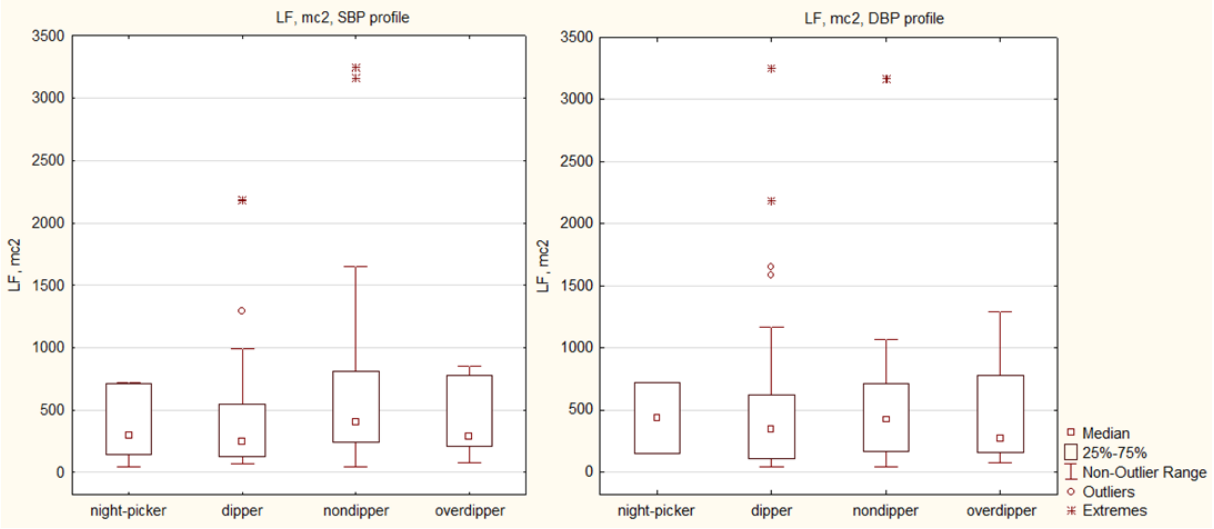

Fig. 3. The low-frequency component (LF) of the HRV, depending on the type of daily profiles of SBP and DBP

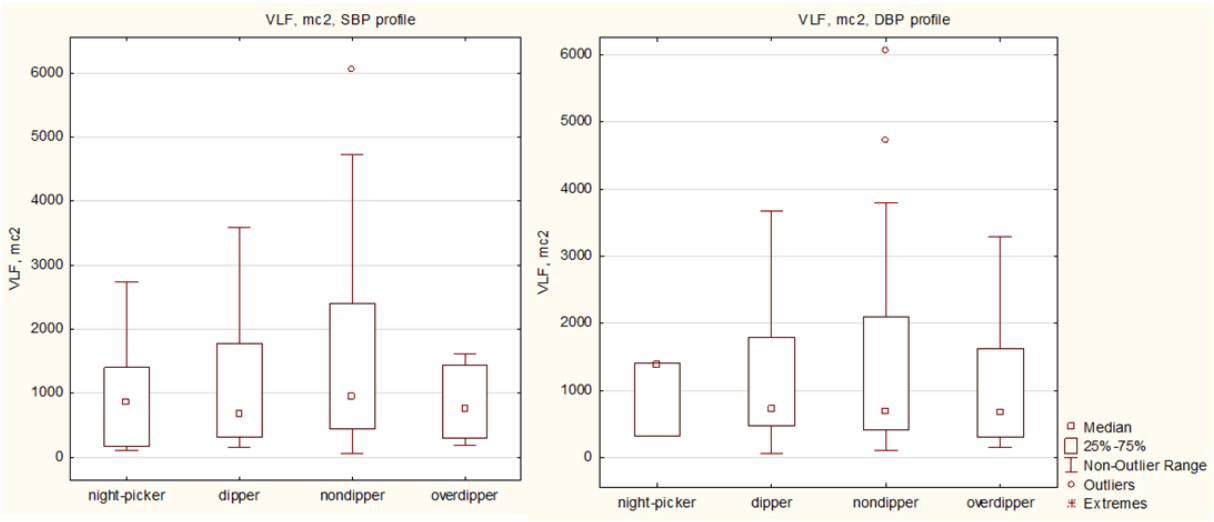

Fig.4. The very low-frequency component (VLF) of the HRV, depending on the type of daily profiles of SBP and DBP

The obtained results in general do not differ from those presented by other authors [8–9]. The analysis of our data confirms that in patients with AH the total power of the HRV decreases, primarily due to the HF component. However, there appears to be no data on HRV particular qualities in patients with AH, dependently of BP profile. The differences we found in HRV parameters in patients with AH in groups of BP daily profile types can be explained by the predominance of the sympathetic branch of regulation in the formation of pathological types of SBP and humoral factors predominance in the formation of pathological types of DBP.

CONCLUSIONS

1. Changes in HRV in patients with AH present with decreased total power with a violation in the ratio of the very low, low and high frequency components, enhanced sympathetic tone and influence of humoral factors.

2. Disorders of SBP daily profile are mainly characterized by increased low frequency component, which indicates an increase in sympathetic and a decrease in parasympathetic influences. Disorders of DBP daily profile present with a relative increase in the power of very low frequency component, which indicates an increased humoral influences.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate to study the HRV changes in hypertensive patients with different types of daily BP profile with the use of antihypertensive drugs of different pharmacological groups.

REFERENCES

1. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. / [K. T. Mills, J. D. Bundy, T. N. Kelly et al.]. // Circulation. – 2016. – № 134. – p. 441–450.
2. Martynenko A.V. Heart rate variability: classification and dynamic system analysis / A.V. Martynenko, M.I. Yabluchansky // Journal of V. N. Karazin` KhNU, Series «Medicine». – 2005. – Issue 11. – P. 10–18.
3. Schmidt E. Yu. Closed loop biofeedback of heart rate variability and paced breathing efficacy evaluation in patients with arterial hypertension / E. Yu. Schmidt, A. L. Kulyk, A.V. Martynenko [et al.] // Journal of V. N. Karazin` KhNU, Series «Medicine». – 2011. – Issue 22. – P. 63–67.
4. Tomina O. E. Heart rate variability in patients with hypertension, comorbid with peptic ulcer disease, taking into account circadian systolic blood pressure / O. E. Tomina, O. Yu. Bichkova, G. M. Fomych [et al.] // Journal of V. N. Karazin` KhNU, Series «Medicine». – 2012. – Issue 24. – P. 52–62.

5. 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 // Journal of V.N. Karazin` KhNU, Series «Medicine». – 2016. – Issue 31. – P. 10–17.
6. 2013 ambulatory blood pressure recommendations for the Diagnosis of Adult Hypertension, Assessment of Cardiovascular and other Hypertension-associated Risk and Attainment of Therapeutic Goals / [R. C. Hermida, M. H. Smolensky, D. E. Ayala et al.] // Chronobiology International. – 2013. – № 30. – p. 55–410.
7. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. // Circulation. – 1996. – № 93. – p. 1043–1065.
8. Singh J. P. Reduced Heart Rate Variability and New-Onset Hypertension. Insights Into Pathogenesis of Hypertension: The Framingham Heart Study / Jagmeet P. Singh, Martin G. Larson, Hisako Tsuji [et al.] // Hypertension. – 1998 – Issue 32. – P. 293–297.
9. Carthy E. R. Autonomic dysfunction in essential hypertension: A systematic review. / Elliott R. Carthy // Annals of Medicine and Surgery. – 2014. – Issue 3. – P. 2–7.

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THE CONTENT OF MCP-1 AND MMP-9 IN BLOOD SERUM OF PATIENTS WITH CHRONIC POLYPOID RHINOSINUSITIS

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The content of MCP-1 and MMP-9 in blood serum of patients with chronic polypoid rhinosinusitis was studied. It was found that this pathology led to a significant increase in MCP-1, which is a marker of fibrosis, in blood serum. The compensatory increase in MMP-9, serving as an antifibrotic factor, is much weaker. Such imbalance between profibrotic MCP-1 and antifibrotic MMP-9 indicates a lack of compensatory adaptation mechanisms of fibrolysis activation and contributes to the development of fibrosis in chronic polypoid rhinosinusitis.

KEY WORDS: chronic polypoid rhinosinusitis, monocyte chemoattractant protein-1, MCP-1, matrix metalloproteinase-9, MMP-9

ВМІСТ MCP-1 ТА MMP-9 У СИРОВАТЦІ КРОВІ ПАЦІЄНТІВ З ХРОНІЧНИМ ПОЛІПОЗНИМ РИНОСИНУСИТОМ

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Вивчено вміст MCP-1 і MMP-9 у сироватці крові пацієнтів з хронічним поліпозним риносинусітом. Встановлено, що дана патологія призводить до значного підвищення маркера фіброзу MCP-1 у сироватці крові. Компенсаторне підвищення MMP-9, яка виступає в якості антифібротичного фактора, виражене набагато слабше. Подібний дисбаланс між профібротичним MCP-1 і антифібротичною MMP-9 вказує на недостатність компенсаторних адаптаційних механізмів активації фіброліза і сприяє розвитку фіброзу при хронічному полипозному риносинуситі.

КЛЮЧОВІ СЛОВА: хронічний поліпозний риносинусит, моноцитарний хемоаттрактантний протеїн-1, MCP-1, матриксна металлопротеїназа-9, MMP-9

СОДЕРЖАНИЕ MCP-1 И MMP-9 В СЫВОРОТКЕ КРОВИ БОЛЬНЫХ С ХРОНИЧЕСКИМ ПОЛИПОЗНЫМ РИНОСИНУСИТОМ

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Изучено содержание MCP-1 и MMP-9 в сыворотке крови пациентов с хроническим полипозным риносинуситом. Установлено, что данная патология приводит к значительному повышению маркера фиброза MCP-1 в сыворотке крови. Компенсаторное повышение MMP-9, выступающей в качестве антифибротического фактора, выражено намного слабее. Подобный дисбаланс между профибротическим MCP-1 и антифибротической MMP-9 указывает на недостаточность компенсаторных адаптационных механизмов активации фибролиза и способствует развитию фиброза при хроническом полипозном риносинусите.

КЛЮЧЕВЫЕ СЛОВА: хронический полипозный риносинусит, моноцитарный хемоаттрактантный протеин-1, MCP-1, матриксная металлопротеиназа-9, MMP-9

INTRODUCTION

Chronic rhinosinusitis is one of the most common diseases in otorhinolaryngology that covers up to 11 % of the population of European countries. The disease negatively affects the quality of life of patients. It has an impact on both physical and mental health and leads to a decrease in working efficiency, insomnia [1]. Negative social aspects of chronic rhinosinusitis imply significant costs of the public health system spent on the treatment

of patients with rhinosinusitis. All of the factors mentioned above contribute to the investigation of the pathogenesis of this disease and the development of new treatment strategies.

It has been known that inflammatory pathology of various etiologies is accompanied by changes in the cytokine serum spectrum and activation of enzymes involved in degradation of the extracellular matrix – matrix metalloproteinases (MMPs) [2–5]. One of such cytokines whose expression increases in inflammatory processes is called monocyte chemoattractant protein-1 (MCP-1). In addition to its ability to stimulate the recruitment of new monocytes into the inflammation zone, MCP-1 is capable of inducing the expression of collagen molecules, acting as a profibrotic factor. Thus, it can serve as a marker of fibrosis [6].

MMPs, in particular matrix metallo-proteinase-9 (MMP-9), have collagenase activity and, accordingly, are involved in breakdown of connective tissue structural components [7]. Thus, MMP-9 is considered to be an antifibrotic factor. Chronic inflammatory processes are known to be accompanied by proliferation of the connective tissue whose intensity depends primarily on the balance between pro - and antifibrotic factors. Features of the content of the abovementioned factors in chronic polypoid rhinosinusitis should be elucidated.

OBJECTIVE

The aim of the study was to study the content of the profibrotic factor MCP-1 and the antifibrotic protease MMP-9 in blood serum of patients with chronic polypoid rhinosinusitis.

MATERIALS AND METHODS

Forty individuals who were treated in the department of otorhinolaryngology at Kharkiv Regional Clinical Hospital were examined. Polypoid form of chronic rhinosinusitis was diagnosed in twenty patients. Their diagnosis was verified using scrupulous clinical and anamnestic examination, as well as laboratory and instrumental tests using criteria proposed by the WHO expert committee. The control group consisted of twenty conditionally healthy individuals with deviated nasal septum without signs of pathology of other organs and systems.

The research was carried out in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki)* and *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (ETC 164)*. The informed consent of patients was obtained for the research. The privacy rights of patients were taken into account.

Samples of venous blood were collected for biochemical tests on an empty stomach in representatives of both groups. The blood was centrifuged for 15 minutes at 3,000 rpm to obtain blood serum. The MCP-1 concentration in blood serum was determined by enzyme-linked immunosorbent assay kits manufactured by eBioscience (Vienna, Austria). To study the content of MMP-9 in the blood serum, the ELISA kit produced by eBioscience (Vienna, Austria) was used. The optical density of the solutions was determined using the Awareness Technology Stat Fax 303 Plus Microstrip Reader.

The data obtained as a result of our research were statistically processed by the GraphPad Prism 5 application using the Student's t-test. Difference between groups was considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Determination of blood serum MCP-1 levels in patients with chronic polypoid rhinosinusitis demonstrated a more than sevenfold increase in this parameter compared to the control group (Table). It has been known that this chemokine is involved in fibrillogenesis of collagen [8, 9] and, therefore, is able to promote proliferation of the extracellular matrix. Thus, the increase in MCP-1 concentrations in the serum of patients with polypoid rhinosinusitis indicates the activation of fibrotic processes.

Given that the intensity of fibrotic changes depends on the balance between profibrotic and antifibrotic factors, we studied the blood serum MMP-9 levels in patients for a complex evaluation of the fibrosis-fibrolysis system in chronic polypoid rhinosinusitis. The choice of MMP-9 can be explained by the ability of this proteolytic enzyme to degrade various types of collagen, thereby mediating fibrolysis [10] and leveling the profibrotic effect of MCP-1.

It was established that MMP-9 blood serum concentrations in patients with the polypoid form of chronic rhinosinusitis were 1.5-fold

higher compared to the same parameter of the control group (Table). Similar changes in the serum content of MMP-9 can be due to its compensatory activation in response to an increase in MCP-1 levels and subsequent intensification of MCP-1-dependent fibrosis. The shift of equilibrium in the fibrosis-fibrolysis system towards the former leads to the corresponding adaptive overproduction of antifibrotic factors. However, we can notice insufficient activation of the metalloproteinase-mediated link of the antifibrotic system in patients with chronic polypoid rhinosinusitis, which indicates a near exhaustion of compensatory capabilities and the shift of equilibrium towards the development of sclerosis.

Table

The content of MCP-1 and MMP-9 in blood serum of patient's chronic polypoid rhinosinusitis (M ± m)

Indices, units	Control group	Patients with chronic polypoid rhinosinusitis
	n = 20	n = 20
Monocyte chemoattractant protein-1 (MCP-1), pg/ml	50.74 ± 0.74	351 ± 40.98 p < 0.001
Matrix metalloproteinase-9 (MMP-9), ng/ml	3.28 ± 0.47	4.81 ± 0.19 p < 0.05

Note: p is a significance value compared to the control group

CONCLUSIONS

1. Chronic polypoid rhinosinusitis is accompanied by an increase in blood serum MCP-1 levels in patients, which indicates the involvement of this chemokine in the proliferation of connective tissue in this pathology.

2. High levels of the antifibrotic proteolytic enzyme MMP-9 are observed in blood serum of patients with chronic polypoid rhinosinusitis, which can serve as a sign of the activation of compensatory adaptive mechanisms aimed at inhibiting the extracellular matrix proliferation.

3. The pronounced increase in MCP-1 levels against the background of a slight activation of MMP-9 in the blood serum of patients with chronic polypoid rhinosinusitis indicates insufficiency of compensatory mechanisms and activation of fibrosis.

PROSPECTS FOR FUTURE STUDIES

It seems to be promising to study other factors that affect the intensity of proliferation of connective tissue in chronic polypoid rhinosinusitis.

REFERENCES

1. Chronic rhinosinusitis in European underestimated disease / [D. Hastan, WJ Fokkens, C. Bachert, RB Newson, J. Bislimovska, A. Bockelbrink, et. al.] // A GA2LEN study. Allergy. – 2011. – Vol. 66(9). – P. 1216–1223.
2. Nissinen L, Kähäri VM. Matrix metalloproteinases in inflammation / L. Nissinen, VM. Kähäri // Biochim et Biophys Acta. – 2014. – Vol. 1840(8). – P. 2571–2580.
3. Cytokine correlation between sinus tissue and nasal secretions among chronic rhinosinusitis and controls / [Oyer S.L., Mulligan J.K., Psaltis A.J., et al.] // Laryngoscope. – 2013. – Issue 123. – P. 72–78.
4. Tkachenko A. S. Osoblyvosti bilkovoho spektru i tsytokinovoho skladu syrovatky krovi shchuriv pry khronichnomu karahenan-indukovanomu intestynal'nomu zapalenni / A. S. Tkachenko, T. V. Gorbach, O. M. Ponomarenko // Aktual'ni pytannya farmatsevtychnoyi i medychnoyi nauky ta praktyky. – 2014. – 1 (14). – P. 73–75.
5. Tkachenko A. S. Vlijanie FNO-α na aktivnost' kinazy 1, regulirujushhej apoptoticheskij signal (ASK-1), pri jeksperimental'nom karraginan-inducirovannom vospalenii / A. S. Tkachenko, T. V. Gorbach, M. A. Tkachenko // Aktual'nye problemy mediciny : Respublikanskaja nauchno-prakticheskaja

konferencija s mezhdunarodnym uchastiem, Gomel', November 3–4, 2016. – Gomel' : GomGMU, 2016. – P. 136–140.

6. Kravchun P. G. Monocitarnij hemoatraktantnij proteïn-1 i matriksna metaloproteïnaza-9 u hvorih iz kardiorenal'nim sindromom 2 tipu na tli hronichnoï sercevoï nedostatnosti ta cukrovogo diabetu 2 tipu zalezhno vid shvidkosti klubochkovoï fil'traciï / P. G. Kravchun, A. V. Narizhna, N. G. Rindina // Zaporozh. med. zhurn. – 2014. – № 5. – P. 24–27.
7. Zhukov, V. I. Uroven' faktora nekroza opuholej al'fa i aktivnost' matriksnoj metalloproteinazy – 2 pri hronicheskom karragenan-inducirovannom gastrojenterokolite / V. I. Zhukov, A. S. Tkachenko // Nauch. vedomosti BelGU. Serija: Medicina. Farmacija. – 2014. – № 18 (189). – P. 122–126.
8. Diminished induction of skin fibrosis in mice with MCP-1 deficiency / [AM. Ferreira, S. Takagawa, R. Fresco, X. Zhu, J. Varga, LA. DiPietro] // J Invest Dermatol. – 2006. – Vol. 126(8) – P. 1900–8.
9. Tesch G. H. MCP-1/CCL2: a new diagnostic marker and therapeutic target for progressive renal injury in diabetic nephropathy American Journal of Physiology – Renal Physiology. – 2008. – Vol. 294 (4). – P. 697–701.
10. Nakonechnaya O. A. Soderzhanie interleykina-8 i matriksnoy metalloproteinazyi-9 v krovi bolnyih s obostreniem hronicheskogo gnoynogo i polipoznogo rinosinuita / O. A. Nakonechnaya, A. I. Onischenko // Aktualnyie problemyi meditsinyi: Respublikanskaya nauchno-prakticheskaya konferentsiya s mezhdunarodnyim uchastiem, Gomel, November, 3–4 2016. – Gomel: GomGMU, 2016. – P. 101–106.

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THE INFLUENCE OF ANXIETY AND DEPRESSIVE CONDITIONS ON AFTERINFARCTION REMODELING IN PATIENTS WITH STEMI

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Depression after AMI increases the frequency of re-hospitalization because of acute coronary syndrome, heart failure, MI, and is a risk factor for cardiac arrest and death. The objective of the study was to define the influence of anxiety-depressive disorders (ADD) on afterinfarction remodeling and the participation of sST2 fibrosis factor in this process. 100 STEMI patients were enrolled to the study, 81 (81 %) male and 29 (29 %) female, of average age of 58,94 ± 10,16 years. Examinations were performed twice: during 1–3 days after PCI with infarct-related artery stenting and included clinical-anamnesis data, blood analyses. The sST2 level was defined by immune-fermentative method with usage of «Presage ST2 Assay», Critical Diagnostics, USA. For ADD objectivization, HADS (Heart Anxiety and Depression Scale) and Teylor questionary were used. In 6 month 6-minute walk test and the volume fraction of interstitial collagen (VFIC) were done. Conclusion: ADD in patients with STEMI aggravates the course of postinfarction period and entails the progression of fibrotic-hypertrophic processes and corresponding remodeling of myocardium, decrease of physical tolerance.

KEY WORDS: anxiety-depressive disorders, STEMI patients, sST2, myocardial remodeling

ВПЛИВ ТРИВОЖНО-ДЕПРЕСИВНИХ СТАНІВ НА ПІСЛЯІНФАРКТНЕ РЕМОДЕЛЮВАННЯ У ПАЦІЄНТІВ З ІНФАРКТОМ МІОКАРДА З ПІДЙОМОМ СЕГМЕНТА ST

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Результати досліджень вказують на те, що тривожно-депресивні розлади погіршують перебіг післяінфарктного періоду. Мета роботи: дослідити у хворих на гострий інфаркт міокарда з підйомом ST вплив тривожно-депресивних розладів на післяінфарктне ремоделювання і участь в цьому процесі маркера фіброза sST2. Висновок: тривожно-депресивні розлади обтяжують перебіг післяінфарктного періоду та сприяють посиленню фіброзно-гіпертрофічних процесів.

КЛЮЧОВІ СЛОВА: тривожно-депресивні розлади, інфаркт міокарда з підйомом сегмента ST, sST2, післяінфарктне ремоделювання

ВЛИЯНИЕ ТРЕВОЖНО-ДЕПРЕССИВНЫХ СОСТОЯНИЙ НА ПОСТИНФАРКТНОЕ РЕМОДЕЛИРОВАНИЕ У ПАЦИЕНТОВ С ИНФАРКТОМ МИОКАРДА С ПОДЪЕМОМ СЕГМЕНТА ST

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Результаты исследований указывают на то, что тревожно-депрессивные расстройства ухудшают течение постинфарктного периода. Цель работы: определить у больных острым инфарктом миокарда с подъемом сегмента ST влияние тревожно-депрессивных расстройств на постинфарктное ремоделирование и участие в нем маркера фиброза sST2. Вывод: тревожно-депрессивные расстройства утяжеляют течение постинфарктного периода и влечет за собой усиление фиброзно-гипертрофических процессов.

КЛЮЧЕВЫЕ СЛОВА: тревожно-депрессивные расстройства, инфаркт миокарда с подъемом сегмента ST, sST2, постинфарктное ремоделирование

INTRODUCTION

Acute myocardial infarction (AMI) is the main reason of mortality and morbidity in Ukraine and in all around the world. AMI mortality remains quite high and hospital mortality is 6–14 % [1–2], research of the factors, which contribute to AMI genesis and its pathogenesis is relevant. Depression and anxiety in European Society of Cardiologists due to cardiovascular prophylactics (2016) are considered as independent risk factors of Ischemic heart disease development. In the INTERHEART research, conducted in 52 countries, anxiety and depression hold the third place among myocardial infarction (MI)-associated risk factors [3]. The prevalence of depressive disorders during one year after AMI is 22,7 %–54 %, depression after AMI increases the frequency of re-hospitalization because of acute coronary syndrome, heart failure, MI, and is a risk factor for cardiac arrest and death [4–7]. The level of mortality in patients with MI with depression is 2–3 times higher than in patients without depression [8].

Multitude of regulatory systems, which are very sensitive to psychoemotional factors interact in the MI pathogenesis. Immuno-inflammatory reaction in AMI is integral component of response on damage of myocardium. It is involved in acute period in processes of survival of cardiomyocytes, apoptosis, myocardial contractility modulation, endothelium damage after ischemic event, reparation mechanisms, early and late remodeling. High level of inflammation markers (TNFα, IL6, IL1β, CRP, etc.), found in AMI, reflects expressed intensity of nonspecific immune-inflammation [9]. At the same time the proofs of relations of depression with activation of parameters of immune system – increase of generation of IL6, CRP, TNFα, MIF are present [4–5]. During experiment, acute stress was the starting point for the profibrotic processes in the myocardium [10]. Marker sST2, which is cytokine-related, draws special attention in this case, as a possible link between depression and postinfarction myocardial remodeling. ST2 (stimulating growth factor, expressed by the gene 2), belongs to the interleukin-1 receptors. IL-33 is a ligand for ST, sST2 blocks the cardioprotective effect of this cytokine, contributing to the development of myocardial fibrosis [11]. In single studies, the level of sST2 is increased in patients with myocardial infarction with elevation of ST segment (STEMI), high levels of this cytokine are predictors of cardiovascular death and heart failure after acute ischemic event [12–13]. We can assume the existence of connection between STEMI, anxiety-depressive disorders, sST2 level and after infarction remodeling process, though there are no available written paper works about it.

OBJECTIVE

To define the influence of anxiety-depressive disorders on postinfarction remodeling and the participation of sST2 fibrosis factor in this process, in patients with STEMI.

MATERIALS AND METHODS

100 STEMI patients were enrolled to the study, 81 (81 %) male and 29 (29 %) female, of average age of 58,94 ± 10,16 years. The patients were hospitalized to the intensive care unit of State Institution «National Institute of therapy n.a. L. T. Malaya of NAMS of Ukraine» during 72 hours of STEMI after PCI with stenting of infarction-dependent artery. Coronary intervention was performed in the catheter laboratory of Institute of general and emergency surgery n.a. V. T. Zaitsev. AMI was diagnosed based on clinical, electrocardiographic, biochemical researches data, according to European guidelines on diagnostics and treatment of STEMI (2012) and MOH Ukraine order №455 from 02 Jul 2014. The research was performed according to DoH regulations, the protocol of research was approved by LEC of GI «National Institute of therapy n.a. L. T. Malaya NAMS Ukraine». Re-examination was performed in 6 months after the index event.

The following clinical and biochemical indicators were defined: hemoglobin, blood glucose, creatinine and its clearance by Cockroft-Gault Equation; lipid metabolism markers: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol

(HDLC) by fermentative method. The concentration of low-density lipoprotein cholesterol (LDLC) was calculated by the Friedwald equation, 2004г.

The sST2 level was defined by immune-fermentative method with usage of «Presage ST2 Assay», Critical Diagnostics, USA. Control group, which consisted of 20 practically healthy individuals, the sST2 level was (21,44 ± 8,68) ng/ml.

Echo-CG was performed on «Medison Sono Ace X6» device (Korea) with usage of sensor with ultrasound frequency of 3,5 MHz during first 24 hours from hospitalization. Left ventricular end diastolic volume (LV EDV), left ventricular end systolic volume (LV ESV), left ventricular end diastolic and end systolic diameters (LV EDD, LV ESD), left ventricular myocardial mass (LVMM), left ventricular ejection fraction (LVEF), diastolic dysfunction – maximal rate of early diastolic filling E (m/sec), maximal rate of left atrium diastolic rate A (m/sec), their ratio – E/A were estimated.

Six months later, another examination was performed. They included evaluation of severity of interstitial myocardial fibrosis by an indirect method – by calculating the volume fraction of interstitial collagen (VFIC) [14] and 6-minute walk test.

$$VFIC\ (\%)=(1-1{,}3\times\frac{total\quad voltage\ QRS(mm)\times height(m)}{MMLV(g)})\times 100,$$

where 1,3 is coefficient of recalculation for MMLV.

VFIC in control group was 8,6 ± 2,1 %.

For anxiety-depressive disorders (ADD) objectivization, HADS (Heart Anxiety and Depression Scale) was used. According to it, there are 3 levels of anxiety and depression: 0–7 points – normal, 8–10 points – borderline case and 11–21 point – increased level, [15], in which 40–50 points corresponded very high anxiety level, 25–40 – high, 15–24 – average (with tendency to high level), 5–14 – average (with tendency to low level) and 0–4 – low. Testing of the subjects allowed defining two groups: 1 – with normal or borderline manifestations of anxiety and 2 – with its increased signs.

Statistical data processing was performed with programs Statistica 8.0 (StatSoft Inc, USA), Microsoft Office Excel 2003. Intergroup differences of qualitative signs were valued using Student's T-Test. For all types of analysis, all differences were considered statistically significant with $p < 0,05$.

RESULTS AND DISCUSSION

Table 1 contains the comparative data of clinical, clinical-laboratory and instrumental examination of patients with STEMI in dependence of ADD. The examination was performed on 48–72 hours of STEMI.

In STEMI patients with ADD (48 %) comparing to patients without ADD (51 %) reliable differences of the following parameters were found: gender, MI in anamnesis, complicated MI, HR, MMLV.

Among the examined patients with STEMI male patients (81 %) prevailed compared with female (19 %) patients. Among females, ADD was diagnosed in 31,2 % cases, absence of ADD – in 8 %, among males – 68,7 % and 92 % accordingly. The greater commitment of women with IHD to concomitant ADD is proved in literature: in INTERHEART research the influence of psychological factors and emotional stress on MI genesis and its course was especially expressed in women [16]. In VIRGO research, young women with AMI had higher level of depression and stress and lower level of physical and mental health than men [17]. Big frequency of co-morbid ADD in patients with STEMI in anamnesis (18,3 % и 1,6 % accordingly) corresponds to data about increased probability of development of new cardiovascular events, including re-infarction in patients with depression after MI [4–5, 18].

The HR in STEMI patients with ADD was increased compared to group without ADD ($P = 0,035$). Tachycardia as a sign of hyperactivity of sympathic-adrenal system is typical for AMI and is one of somatic syndromes of ADD. Cumulative effect of these reasons of hypersympathicotonia results in increased need of oxygen for myocardium consumption, and also to development of metabolic and dysfunctional disorders, which complicate the course of MI.

Table 1

Clinical characteristics of patients depending on anxiety and depressive conditions (M ± δ)

Data	Patients with ADD, (n=48)	Patients without ADD, (n=52)	T,χ^2 ,p
Age, years	60,75 ± 10,41	57,27 ± 9,72	0,07
Gender male/female	33(68,7 %) / 15(31,3 %)	48 (92,3) / 4(7,7 %)	9,00 p=0,003
Smoking	18 (37,5 %)	24 (46,2 %)	0,77 p=0,38
Diabetes mellitus	10 (20,8 %)	7 (13,5 %)	0,96 p=0,33
Body mass index	29,93 ± 5,19	29,61 ± 6,08	0,78
MI in anamnesis	9 (18,8 %)	1 (1,9 %)	6,09 p=0,01
Complicated MI	13 (27,1 %)	11 (21,2 %)	0,48 p=0,49
HR, per 1 min	81,14 ± 21,44	73,25 ± 15,12	0,035
SBP, mmHg	141,00 ± 14,21	140,10 ± 27,71	0,88
DBP, mmHg	82,83 ± 45,50	83,12 ± 12,18	0,91
Creatinine clearance, ml/min	77,17 ± 26,38	87,95 ± 28,13	0,047
Glucose, mmol/l in patients with DM	12,91 ± 5,44	11,02 ± 5,98	0,52
Glucose, mmol/l in patients without DM	7,26 ± 2,74	6,53 ± 1,71	0,15
Hemoglobin, g/l	133,43 ± 13,52	140,01 ± 18,19	0,04
Total cholesterol, mmol/l	4,77 ± 1,55	4,77 ± 1,30	0,99
LDL, mmol/l	3,02 ± 1,30	2,83 ± 1,23	0,49
CVHD, mmol/l	0,69 ± 0,47	0,81 ± 0,49	0,25
Triglycerides, mmol/l	1,54 ± 1,05	1,75 ± 1,01	0,35
HDL, mmol/l	1,06 ± 0,29	1,12 ± 0,39	0,43
ST2, ng/ml	76,75 ± 33,54 (n = 28)	76,44 ± 29,44 (n = 35)	0,96
LVEDD, sm	5,20 ± 0,53	5,20 ± 0,49	0,98
LVESD, sm	3,80 ± 0,67	3,78 ± 0,63	0,94
LVEF, %	51,70 ± 10,66	50,72 ± 9,57	0,65
E/A	1,13 ± 0,53	1,20 ± 0,49	0,65
LVMM, g	267,00 ± 79,61	231,27 ± 52,51	0,01

Reliable increase of LVMM in STEMI patients with ADD compared to patients without ADD (P = 0,01) is worth paying attention. This fact can be observed as manifestation, not connected with development of current MI, but caused by the pre-infarction period of left ventricular hypertrophy (LVH) formation. Hypertensive, ischemic lesions of myocardium, AMI in anamnesis and co-morbid ADD and neurochemical, neurohumoral and immunoinflammatory reactions, corresponding to it, take part in this multifactorial process.

In patients with STEMI with ADD the reliable decrease of creatinine clearance (P = 0,047) and hemoglobin level (P = 0,04) is defined, comparing to patients without ADD. Dysfunction of kidneys' functional abilities in AMI with ADD can be a consequence of summarized manifestations of severe cardiac status (re-infarction, complicated MI, diabetes mellitus (DM) with ADD symptoms, which negatively affects the glomerular apparatus of kidneys through multiple regulatory systems. The decrease of hemoglobin level in patients with STEMI and ADD was within the limits of normal values and requires further research and analysis.

Positive correlations between anxious states with female gender, (r = 0,47, P = 0,004), MI in anamnesis, (r = 0,47, P=0,005), systolic blood pressure (SBP), (r = 0,23, P = 0,081), diastolic blood pressure (DBP), (r = 0,31, P = 0,071) were found.

Tendency in differences between first and second groups of patients was found in the following indicators: smoking, DM, complicated infarction. In relation to connection of smoking and ADD in patients with STEMI, the following data was received: tendency of patients without ADD to smoke more (46,2 %), than with ADD (37,5 %), P = 0,38. The same data was retrieved by authors, who position smoking as a way to deal with stress [19]. Diabetes mellitus among patients with STEMI

and ADD was diagnosed in 20,8 % cases, without ADD – 13,5 %, P = 0,33. ADD in DM patients happens 10–20 % more frequent, than in general population, etiopathogenetic connection between affective disorders and DM is being implemented through the activation of hypothalamic-pituitary-adrenal system, resistance to insulin, cytokines [20]. That is why most frequency of ADD in STEMI patients and DM compared to patients without DM is totally reasonable. Complicated MI (acute decompensate heart failure, cardiac asthma, pulmonary edema, aneurism of heart, ventricular or supraventricular rhythm disorders) were observed in 27,1 % patients with co-morbid ADD and 21,2 % – without ADD. That's why the connection between ADD and factors, contributing to the complicated course of MI is quite possible.

There were no differences between 1 and 2 groups of STEMI in dependence of ADD on such parameters: age, BMI, SBP, DBP, blood glucose, lipid specter, level of sST2.

sST2 level in general group of patients STEMI was 76,58 ± 25,63, significally exceeding the value of the parameters of control group (P = 0,04), correlation between sST2 and complicated MI, (r = 0,39, p = 0,056), heart rate (HR), (r = 0,34, p = 0,094), LV EDD (r = 0,64, p = 0,01), LVEF, (r = -0,59, p = 0,02), LVMM, (r = 0,57, p = 0,042) were found. Depending on the presence of ADD, no differences in values of sST2 in acute period of STEMI were found.

After six months after index event, 46 patients with ADD and 51 – without it were examined. During this period, 3 patients died, 2 re-infarctions were diagnosed. In table 2 the structure and functional data of patients with STEMI depending on ADD presence are presented.

Table 2

Structure and functional data of patients in 6 month after STEMI depending on anxiety and depressive conditions (M ± δ)

Data	Patients with ADD N = 46	Patients without ADD N = 51	P
HR, per min	79,19 ± 16,14	71,18 ± 21,12	0,04
SBP, mm Hg	140,38 ± 44,54	134,62 ± 21,31	0,41
DBP, mm Hg	80,33 ± 38,50	78,43 ± 22,28	0,76
LV EDD, sm	5,58 ± 0,74	5,29 ± 0,67	0,045
LV ESD, sm	4,03 ± 1,04	3,96 ± 0,77	0,78
LVMM, g	274,72 ± 95,47	240,08 ± 70,27	0,043
LVEF, %	50,61 ± 38,50	53,93 ± 12,71	0,34
E/A	1,20 ± 0,62	1,31 ± 0,66	0,55
6-minute walk test, m	405,15 ± 105,29	480,30 ± 79,73	0,02
VFIC, %	28,06 ± 7,10	19,81 ± 6,80	0,042
sST2, ng/ml	35,58 ± 11,36	30,18 ± 9,79	0,047

After six months after index event, there was a difference between patients with ADD and patients with normal psychological status: significantly different HR (P = 0,09), LV EDD (P = 0,095), LVMM (P = 0,043), 6-minute walk test results (P = 0,02), VFIC (P = 0,042), sST2 level (P = 0,047).

In the literature you can find contradictory data about connection between ADD and structural and functional disorders of myocardium after endured AMI, the association between LVEF and ADD was the main topic [5, 18]. Significant increase of following markers, such as LV EDD, LVMM in patients with STEMI with ADD comparing to patients without ADD shows the influence of ADD on the process of post-infarction remodeling of myocardium (LVH), dimensions of the cavity of the left ventricle), also the values of LVEF and diastolic function of myocardium in compared groups had no differences. Negative influence of ADD on functional status of AMI eST patients is represented by 6-minute walk test results – in the first group, physical exercise tolerance corresponded II functional class(FC) of CHD, in the second – I FC (P = 0,02). These results are consistent with literature data about decreased physical exercise tolerance (by the results of 6-minute walk test) in IHD patients with ADD compared to comparable (in severity of IHD) group with normal psychological status [5,7].

Pathogenic mechanisms of negative ADD influence on post-infarction remodeling of myocardium are researched insufficiently. One of the markers of myocardium fibrosis is ST2, which is actively involved in the development of remodeling of myocardium and its function amongst with IL-33. ST2 is expressed from cardiomyocytes and fibroblasts as membrane-bound isoform (ST2L) and soluble isoform (sST2). Its ligand, IL-33, is expressed from cardiomyocytes and fibroblasts, and during increased pressure loading, interacting with ST2L, has a cardioprotective effect – decreases myocardial fibrosis, hypertrophy of cardiomyocytes, apoptosis, improves myocardial functions. In response to the stress and myocardial damage, sST2 is expressed in cardiomyocytes, fibroblasts, endothelium cells of microvascular system of myocardium, which works as a «bait-receptor» for IL-33 and decreases their cardioprotective effect by disrupting the system of interaction with ST2L. Increased genesis of sST2 leads to amplification of LVH, fibrosis, apoptosis, pathological remodeling of myocardium, decreased functional ability of myocardium and progression of the disease [11]. In some researches sST2 in STEMI, its increased level on hospitalization was associated with increased risk of death and heart failure, was risk factor of death in 30 days, had correlation with post-infarction remodeling [12].

The results of this study showed a significant increase of sST2 level in STEMI in both groups. It reflects the response on the stress damage of cardiomyocytes due to myocardial necrosis. In the acute period of STEMI, there were no differences in groups with or without ADD. In 6 months after the event, the patients with MI and ADD had sST2 level decreasing to a lesser extent, than without ADD (55 % and 61 % accordingly, P = 0,047). Combination of higher values of sST2 in group with ADD with increased dilatation and hypertrophy of left ventricle (LV EDD, LVMM), decrease of physical exercise tolerance (6-minute walk test) is an evidence of the existence of a bond between sST2, post-infarction remodeling and presence of ADD.

The comparison of the VFIC marker in myocardium in 6 months after STEMI discovered its significant increase compared to control in groups 1 and 2 (P = 0,03; P = 0,041), the level in ADD patients was higher than in patients without ADD (P = 0,042).

The positive correlation between sST2 during hospitalization and VFIC in six months after index event, (r = 0,51, P = 0,009), may evidence that its prognostic value for the development of fibrotic changes in myocardium and negative influence on the process of post-infarction remodeling and functional abilities of myocardium.

CONCLUSIONS

1. STEMI patients have ADD frequency of 48 %, positive relation between ADD and female sex, previously diagnosed myocardial infarction, heart rate, left ventricle myocardium mass, negative – with functional state of kidneys and hemoglobin level.

2. ADD in patients with STEMI aggravates the course of postinfarction period and entails the progression of fibrotic-hypertrophic processes and corresponding remodeling of myocardium, decrease of physical tolerance.

PERSPECTIVES OF FURTHER RESEARCH

Prospects for future studies is to estimate the prevalence of genetic polymorphism genes of RAAS – AT II R1 (A1166C), CYP11B2 (C344T) in investigated patients with STEMI, their connection with sST2 and association with phenotypic signs of MI and ADD.

REFERENCES

1. Véronique L. Roger, Alan S. Go, Donald M. Lloyd-Jones, et al. Heart Disease and Stroke Statistics – 2012 Update A Report From the American Heart Association // Circulation. 2012. Vol. 125(1). P.e2–e220.
2. McManus D.D., Gore J., Yarzebski J. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI // Am J Med. – 2011. – Vol.124(1). P. 40–7. doi: 10.1016/j.amjmed.2010.07.023.
3. Yusuf S., Hawken S., Ounpuu S. et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study // Lancet. – 2004. – Vol. 364(9438). – P. 937–52.

4. Pogosova N. V., Saner H., Pedersen S. S. i dr. Psihosotsialnyie aspektyi v kardiologicheskoy reabilitatsii: ot teorii k praktike. Konsensusnyiy dokument sektsii po kardiologicheskoy reabilitatsii Evropeyskoy assotsiatsii po kardiovaskulyarnoy profilaktike i reabilitatsii Evropeyskogo obschestva kardiologov // Kardiologiya. – 2016. – № 10. – P. 96–108.
5. Vasyuk Yu. A., Lebedev A. V. Depressiya, trevoga i infarkt miokarda: vse tolko nachinaetsya // Ratsionalnaya farmakoterapiya v kardiologii. – 2007. – № 3. – P. 41–51.
6. Shimohina N. Yu. Rol trevozhno-depressivnyih rasstroystv v patogeneze ostrogo koronarnogo sindroma // Sibirskoe meditsinskoe obozrenie. – 2014. – № 2. – P. 47–52.
7. Kovalenko V. M., Dolzhenko M. M., Nesukay O. G., Nudchenko O. O., Lur'i S. Z. na cholI grupi doslIdnikiv Poshirenist trivozhno-depresivnih rozladiv ta iih vpliv na sertsevo-sudinnI faktori riziku za danimi doslidzhennya EUROASPIRE IV-PRIMARY CARE v Ukraini // Arterialnaya gipertenziya. – 2015. – № 6(44). – P. 24–28.
8. Oganov R. G., Pogosova G. V., Shalnova S. A. Depressivnyie rasstroystva v obschemeditsinskoy praktike po dannyim issle- dovaniya KOMPAS: vzglyad kardiologa // Kardiologiya. – 2005. – № 8. – P. 6–9.
9. Tian R., Gonglin Hou, Dan Li, et al. A possible change process of inflammatory cytocins in the prolonged chronic stress and its ultimate implications for health // The Scientific World Journal. – 2014. – Article ID 780616, – 8 pages.
10. Werner G. S., Surber R., Ferrari M., Fritzenwanger M., Figulla H. R. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction // Eur. Heart J. – 2006. – Vol. 27(20). – P. 2406–2412.
11. Villacorta A., Maisel A.S. Soluble ST2 testing: a promising biomarker in the management of heart failure //Arq Bras Cardiol. – 2016. – Vol. 106(2). – P. 145–152. DOI:10.5935/abc.20150151.
12. Hamm C. W., Bassand J. P., Agewall S. et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation // European Heart Journal. – 2012. – Vol.33. – P. 2569–2619.
13. Weir R.A., Miller A.M., Murphy G.E. et al. Serum soluble ST2 // J Am Coll Cardiol. – 2010. – Vol.55. – P. 243–250.
14. Shirani J., Pick R., Quo Y., Silver M.A. Usefulness of the Electrocardiogram and Echocardiogram in predicting the amount of interstitial myocardial collagen in endomyocardial biopsy specimens of patients with chronic heart failure // Am. J. Cardiol. – 1992. – Vol.69. – P. 1502.
15. Taylor J. A. A Personality Scale of Manifest Anxiety // J. Abnormal and Social Psych. – 1953. – Vol. 48, Suppl.2. – P.285–290.
16. Anand S.S., Islam S., Rosengren A. et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study // Eur Heart J. – 2008. – Vol.29, Suppl.7. – P. 932–940.
17. Bucholz E.M., Strait K.M., Dreyer R.P. et al. Sex differences in young patients with acute myocardial infarction: A VIRGO study analysis // Eur Heart J Acute Cardiovasc Care. – 2016 Aug 2. pii: 2048872616661847.
18. Omelyanenko M.G., Shumakova V.A., Suhovey N.A. i dr. Psihoemotsionalnyie narusheniya i endotelialnaya disfunktsiya v razvitii serdechno-sosudistyih zabolevaniy, assotsiirovannyih s aterosklerozom // Sibirskiy meditsinskiy zhurnal. – 2014. – Vol. 29, – № 3. – P.18–24.
19. Kornatskiy V. M. [The problem of cardiovascular diseases and ways to minimize them in Ukraine] // Kardiologiya: ot nauki k praktike. – 2013. – № 5. URL http://kardiolog.in.ua/5-07-2013/172-problema-boleznei-sitemu-krovoobrascheniya.
20. Kovalev Yu. V., Zelenin K. A. Saharnyiy diabet i trevozhnyie rasstroystva // Meditsinskaya psihologiya v Rossii: elektron. nauch. zhurn. – 2011. – № 5. URL: http:// medpsy.ru.

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DISTRIBUTION OF QT DURATION ACCORDING TO AMBULATORY ECG MONITORING DATA IN PATIENTS WITH HYPERTENSION DEPENDING ON CLINICAL MANIFESTATIONS

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The study was carried out to identify the distribution of QTc during ECG AM depending on clinical features of EH in 82 patients. As classified shortened was considered QTc < 320 ms, as normal > 320 ms and < 440 ms, as classified prolonged was considered QTc > 440 ms. Average, maximum and minimum QTc are registered in every patient during ECG AM. The results confirm low probability of short QTc and demonstrate presence of prolonged QTc in every patient during ECG AM. The largest duration of maximal QTc have adulthood male patients with obesity III st., with low and high circadian index, with II stage and mild EH, with for the first time diagnosed EH and with EH lasting more than 10 years, with mild cardiovascular risk, with diffuse cardiosclerosis, with I and II FC and I and IIA st of HF.

KEY WORDS: hypertension, duration of QTc interval, ambulatory ECG monitoring

РОЗПОДІЛ ТРИВАЛОСТІ ІНТЕРВАЛУ QTc ЗА ДАННИМИ АМБУЛАТОРНОГО МОНІТОРУВАННЯ ЕКГ У ХВОРИХ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ В ЗАЛЕЖНОСТІ ВІД КЛІНІЧНИХ ПРОЯВІВ

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Проведено вивчення розподілу тривалості QTc при АМ ЕКГ в залежності від клінічних ознак ГХ у 82 пацієнтів. За класифікований укорочений приймали QTc < 320 мс, нормальний > 320 мс та < 440 мс, класифікований подовжений > 440 мс. У кожного пацієнта за даними АМ ЕКГ зареєстровані середній, максимальний та мінімальний QTc. Результати підтверджують рідку вірогідність укороченого QTc і показують існування подовженого QTc у кожного пацієнта при АМ ЕКГ. Тривалість максимального QTc найбільша у пацієнтів зрілого віку, чоловічої статі, з ожирінням III ст., із зниженим та високим циркадним індексом; II стадією та м'якою ступеню ГХ, з вперше зареєстрованою та більше 10 років ГХ, помірним кардіоваскулярним ризиком серцево-судинних ускладнень, дифузним кардіосклерозом, I і II ФК та I і IIA стадією ХСН.

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, тривалість інтервалу QTc, амбулаторне моніторування ЕКГ

РАСПРЕДЕЛЕНИЕ ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QTc ПО ДАННЫМ АМБУЛАТОРНОГО МОНИТОРИРОВАНИЯ ЭКГ У ПАЦИЕНТОВ С ГІПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ В ЗАВИСИМОСТИ ОТ КЛИНИЧЕСКИХ ПРОЯВЛЕНИЙ

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Проведено изучение распределения продолжительности интервала QTc при АМ ЭКГ в зависимости от клинических признаков ГБ у 82 пациентов. За классифицированный укороченный принимали QTc < 320 мс, нормальный > 320 мс и < 440 мс, классифицированный удлиненный > 440 мс. У каждого пациента по данным АМ ЭКГ зарегистрированы средний, максимальный и минимальный QTc. Результаты подтверждают редкую вероятность укороченного QTc и показывают существование удлиненного QTc у каждого пациента при АМ ЭКГ. Продолжительность максимального QTc наибольшая у пациентов зрелого возраста, мужского пола, с ожирением III ст., с пониженным и высоким циркадным индексом; II стадией и мягкой степенью ГБ, с впервые

зарегистрированной и более 10 лет ГБ, умеренным кардиоваскулярным риском сердечно-сосудистых осложнений, диффузным кардиосклерозом, I и II ФК и I и II А стадией ХСН.

КЛЮЧЕВЫЕ СЛОВА: гипертоническая болезнь, продолжительность интервала QTc, амбулаторное мониторирование ЭКГ

INTRODUCTION

Hypertension (EH) – is one of the most common chronic diseases that significantly increase the risk of cardiovascular complications and sudden death [1–2].

Prolongation or shortening of QT interval is seen as the factor which increases risk of life-threatening arrhythmias [3–6]. Electro-physiological phenomenon of prolonged QT intervals considered to be independent predictor of fatal arrhythmias that leads to sudden cardiac death [7–9].

International guidance on the prevention of sudden cardiac death (SCD) [10] recommends evaluation of QT interval as class 1A indication for the ambulatory ECG monitoring (ECG AM) in risk groups of developing life-threatening arrhythmias.

Ambulatory ECG monitoring is one of the basic methods in identifying this class of arrhythmias [11–12]. We didn't find in the literature any information about the relationship between the distributions of QT duration in ECG AM and clinical signs of EH.

OBJECTIVE

The aim of the work is to study the distribution of QTc duration in ECG AM depending on clinical manifestation of the EH.

The study was conducted as a part of research work «Development and research of automatic control system of heart rate variability», state registration 0109U000622.

MATERIALS AND METHODS

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

Among 82 patients with hypertension the mild hypertension took place in 51, 22 %, moderate – in 29, 27 %, severe – in19, 51 %. The largest proportion of patients with EH II stage was 71, 95 %, I stage – 14, 63 %, III stage – 13, 41 %. The Ischemic heart disease (IHD) was 73,17 % out of the total number of registered patients with EH, among them – 52,44 % diffuse cardiosclerosis (DC), 18,29 % – stable angina (SA), 2,44 % – post infarction cardiosclerosis (PIC). Patients with EH without IHD accounted 26, 83 %. Chronic heart failure (CHF) I stage – 42, 68 %, IIA stage – 30, 49 %. Chronic heart failure with functional class I (CHF FC) was registered in 40,24 %, II class – in 28,05 %, III class –in 4,88 %.

Patients with acute cardiovascular diseases, with stable exertion angina IV FC, HF IIB-III stages and with thyroid diseases were not included in the study.

Identifying of the duration of the medium, maximum and minimum QTc was conducted by results of ECG AM. For these goals we used combined Holter monitoring (ECG + BP). Calculation of QTc duration was carried out with the help of program «Cardio Sense». Corrected QT interval was used (QTc) taking into account the heart rate. Calculation was conducted by Bazzet formula [13–14]. As classified shortened was considered QTc < 320 ms, as normal > 320 ms and < 440 ms, as classified prolonged was considered QTc > 440 ms [6, 12, 15]. These indicators correspond to the resting ECG parameters.

We determined the dependence of average daily indicators of QTc duration in patients with essential hypertension according to gender, age, weight of patients, duration of EH, stage and degree of EH, cardiovascular risk, presence of diabetes, ischemic heart disease, FC HF, stage of HF and the type of circadian index.

Statistical data analysis was performed with applying of parametric criteria (average value – x and standard deviation – s). For determining statistically significant difference in quantitative indicators of QTc in selected groups Student's t-test and multifactor test were used (MANOVA). Calculations were carried out on a personal computer using programs «Microsoft Office Excel 2010» and «STATISTICA 10».

RESULTS AND DISCUSSION

Average, maximum and minimum QTc are registered in every patient during AM ECG. But only by one ECG episode of QTc duration it can't be assigned to the class of normal, prolonged or short QT as in majority of modern researches [6, 9]. That's why it is not

enough and required 24-hours ECG monitoring [6–7, 12].

QTc interval duration of patients with EH during AM ECG in general and depending on age, gender, BMI and circadian index are presented in table 1.

Table 1

QTc interval duration QTc ($\bar{x}$, s) during AM ECG in patients with EH in general and depending on age, gender, BMI and circadian index

Clinical manifestation	Graduation of clinical features	N	P, %	Average QTc, ms		Maximum QTc, ms		Minimum QTc, ms	
				$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s
		82	100	421	18	486	31	382	27
Age, years	Adulthood	35	43	416*	18	487*	34	379 *	26
	Old age	47	57	398*	18	457*	29	361*	27
Gender	Female	54	66	426*	18	490	31	385	27
	Male	28	34	411*	19	497	32	377	27
BMI, kg/m^2	Normal weight	9	11	420	20	479	40	391	16
	Overweight	27	33	418	18	480	33	384	22
	Obesity I	27	33	421	20	491	28	379	34
	Obesity II	14	17	422	15	491	31	380	28
	Obesity III	5	6	431	22	495	25	381	16
Circadian index	Normal	40	49	419	20	484	37	384	23
	Low	38	46	424	17	487	24	381	32
	High	4	5	419	11	488	17	378	11

*Note: N – number of surveys; P – specific gravity; $\bar{x}$ – arithmetic mean; s – standard deviation; QTc – corrected QT; * – $p < 0,05$ – between QTc values in clinical groups.*

In all patients in group the only episode of shortened QTc was registered, the duration of average and minimum QTc are within normal range, while maximum QTc significantly exceeds the normal range. In adulthood patients maximum and minimum QTc were registered, but in aged patients – minimum QTc. Female patients had more prolonged average QTc, but male patients had more prolonged maximum and minimum QTc. In case of obesity of III degree average and maximum QTc intervals are more prolonged, while in case of obesity of I degree the least QTc was minimum. The longest duration of average QTc is in patients with low circadian index (CI), of maximum – in patients with low and high, and minimum duration of average QTc is in patients with high circadian index.

QTc interval duration QTc ($\bar{x}$, s) during ECG AM in patients with EH depending on stage and degree of EH, duration of the disease and cardiovascular risk are presented in tab. 2.

Table 2

QTc interval duration QTc ($\bar{x}$, s) during AM ECG in patients with EH depending on stage and degree of EH, duration of the disease and cardiovascular risk

Clinical manifestation	Graduation of clinical features	N	P, %	Average QTc, ms		Maximum QTc, ms		Minimum QTc, ms	
				$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s
Stages of EH	I	12	15	409	13	480	34	371*	16
	II	59	72	423	18	492	30	383*	29
	III	11	13	422	19	464	25	392*	21
Degrees of EH	Mild	42	51	417*	17	489	31	381	22
	Moderate	24	29	421*	17	484	30	382	33
	Severe	16	20	430*	22	484	35	386	29
Duration, years	For the first time	7	8	418	6	494	32	374	21
	0–5	31	38	418	18	489	31	381	27
	6–10	23	28	420	18	474	20	383	26
	>10	21	26	426	21	494	39	386	30
Cardiovascular risk	Low	11	13	422	19	464	25	392	21
	Moderate	50	61	420	19	488	34	378	29
	High	13	16	424	18	484	29	386	29
	Very high	11	13	422	19	464	25	392	21

*Note: N – number of surveys; P – specific gravity; $\bar{x}$ – arithmetic mean; s – standard deviation; QTc – corrected QT; * – $p < 0,05$ – between QTc values in clinical groups***.**

The longest average daily and maximum QTc were recorded in group with EH II stage, minimum was in patients with EH I stage. An increase of average QTc duration was correlated with an increasing degree of hypertension. The longest duration of the maximum and minimum QTc was observed in patients with mild hypertension. Patients with course of the disease more than 10 years had the highest rates of average daily and maximum QTc, patients with EH diagnosed for the first time had maximum and minimum QTc. The duration of average daily QTc is longer in patients with high cardiovascular risk, while the duration of maximum and minimum QTc are longer in patients with mild cardiovascular risk.

QTc interval duration QTc ($\bar{x}$, s) during AM ECG in patients with EH depending on IHD, HF stage and FK of HF, presence of diabetes mellitus are presented in Table 3.

Table 3

QTc interval duration QTc ($\bar{x}$, s) during AM ECG in patients with EH depending on IHD, HF stage and FK of HF, presence of diabetes mellitus

Clinical manifestation		Graduation of clinical features	N	P, %	Average QTc, ms		Maximum QTc, ms		Minimum QTc, ms	
					$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s
IHD		In total	60	73	416	19	478	30	376	28
		Stable angina	15	18	417	20	475	37	377	29
		Diffuse cardiosclerosis	43	53	424	18	491	26	384	28
		Focal cardiosclerosis	2	2	425	12	478	20	396	13
		Absence of IHD	22	27	416	17	487	37	382	25
CHF	FC	I	23	28	425	18	487	24	384	33
		II	33	40	420	19	486	34	379	23
		III	4	5	429	20	484	12	403	26
	Stage	I	35	43	425	19	483	31	382	30
		II A	25	30	420	18	483	31	382	24
Diabetes mellitus		DM 2 type	11	13	426	18	484	17	399	19
		Absence of DM	71	87	420	18	487	33	381	27

*Note: N – number of surveys; P – specific gravity; $\bar{x}$ – arithmetic mean; s – standard deviation; QTc – corrected QT; * – p < 0,05 – between QTc values in clinical groups.*

In patients with focal cardiosclerosis the largest was average daily QTc, with diffuse cardiosclerosis (DC) – the maximum QTc and with stable angina – the minimum QTc. The longest duration of average daily QTc was observed in patients with HF FC III, and uniformly the same duration of QTc was observed in patients with FC I, I stage of HF and FC II, IIA stage of HF. The duration of the maximum interval QTc was the largest in patients with I and II FC of HF, and uniformly the same – in patients with FC III and I and IIA stages of HF; the duration of the minimum interval QTc was the least in patients with FC II of HF. The duration of average daily and maximal QTc more often was recorded in patients with DM, and minimal QTc interval – in patients without DM [16].

Student's t-test for independent groups showed that for grouping sign «stages of EH», accurately different at level $p < 0,05$ is minimal QTc, and for grouping sign «degrees of EH» – minimal QTc. Multifactorial test (MANOVA) confirms that researched effects are significant on level $p < 0,05$.

In all the above data accurate difference at level $p < 0,05$ between the average and the maximum QTc; between the average and minimum QTc; between the minimum and the maximum QTc is observed. That's why the corresponding marks are not put anywhere in the tables.

Therefore, obtained results not only confirm a rare probability of short QTc [4–5, 13], but also show presence of prolonged QTc in every patient during ECG AM. Based on the abovementioned it is necessary to use ECG AM in clinical practice to evaluate QTc duration in patients with EH. But such works have not been conducted before. Obviously, specific gravity of prolonged QTc during 24-hours must be the most important, but it requires further study.

CONCLUSIONS

1. Average, maximum and minimum QTc are registered in every patient during ECG AM. At the same time the average and minimum QTc are within normal ranges while maximum QTc far exceeds it.

2. The largest duration of maximal QTc have adulthood male patients with obesity III st., with low and high circadian index, with II stage and mild EH, with for the first time diagnosed EH and with EH lasting more than

10 years, with mild cardiovascular risk, with diffuse cardiosclerosis, with I and II FC and I and IIA stage of HF.

3. The presence of critical level of maximum indicators of the QTc duration in each patient with EH demonstrates the need to use ECG AM in its evaluation taking into account the specific gravity per day.

PROSPECTS FOR FUTURE STUDIES

The prospect of further research is studying of the relationship between specific gravity of maximum QT min ambulatory ECG monitoring and clinical manifestations in patients with essential hypertension.

REFERENCES

1. Rekomendatsii Yevropeiskoi Asotsiatsii hipertenzii ta Yevropeiskoi Asotsiatsii kardiolohiv (ESH/ ESC) polikuvanniuAH, 2013.
2. Rekomendatsii Ukrainskoi Asotsiatsii kardiolohiv z profilaktyky ta likuvannia arterialnoi hipertenzii. Posibnyk do Natsionalnoi prohramy profilaktyky i likuvanniaarterialnoihipertenzii. – K.: PP VMB; 2008. – 80 s.
3. Afanaseva T. Yu., Oslopova Yu. V., Terehulov Yu. E., Oslopov V. N. Dolhyi QT. Monohrafyia. – Kazan: MeDDok, 2013. – 208 s.
4. Philippe M. Short QT syndrome. Update on a recent entity / M. Philippe, F. Extramiana, P. Sbragia // Archives of Cardiovascular Disease. – 2008. – № 101. – p. 779–786.
5. Wojciech Z. Long QT Syndrome and Short QT Syndrome / Z. Wojciech // Progress in Cardiovascular Diseases. – 2008. – № 3. – p. 264–278.
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. Yabluchanskyi N. Y., Martыnenko A. V., Martymianova L. A. Ambulatornaia эlektrokardyohrafyia / Seryia: dlia nastoiashchykh vrachei. – Kh. : – KhNU ymeny. V. N. Karazyna, 2015, 113 s.
8. Kovalenko V. M. Nastanova z arterialnoi hipertenzii / V. M. Kovalenko, Ye. P. Svishchenko, Yu. M. Sirenko. – K.: MORION, 2010. – S. 262–269.
9. Grigioni F., Piovaccari G., Boriani G. Prolonged QRS and QTc interval and mortality // Heart. – 2007. – № 93 (9). – P. 1093–1097.
10. Rekomendatsii Asotsiatsii kardiolohiv Ukrainy. Likuvannia shlunochkovykh porushen sertsia ta profilaktyka raptovoi sertsevoi smerti: Kyiv, 2009.
11. Ambulatorne monitoruvannia EKH. Suchasni tekhnolohii, diahnostychni mozhlyvosti, pokazannia. Metodychnyi posibnyk. – Kyivska medychna akademiia pisliadyplomnoi osvity im..P. L. Shupyka. MOZ Urainy, 2004. – S. 30–33.
12. Ambulatorne kholterivske monitoruvannia EKH (proekt rekomendatsii) /Sychov O. S., Lutai M. I., Romanova O. M. ta in. // Ukrainskyi kardiolohichnyi zhurnal. – 2005. – № 5 (dodatok). – S. 11–37.
13. Hiroshi M. The QT syndromes: long and short / M. Hiroshi, W. Jiashin, P. Douglas // Lancet. – 2008. – № 372. – p. 750–763.
14. Moss A. Long QT syndrome |A. Moss J. Robinson // Heart Dis Stroke. – 1992. – № 1. – p. 309–314.
15. Kulyk V. L., Yabluchanskyi M. I. Interval QT v kardiolohichnii klinitsi. / «Visnyk Kharkivskoho natsionalnoho universitetu» – Kh.: – KhNU imeni V. N. Karazina, – 2009. – № 879. – S. 73–96.
16. Radman A. QT interval dispersion in hypertensive diabetics and in patients with hypertension with chronic heart failure without diabetes / A. Radman, J. Murín, J. Bulas, [et al.] // Vnitr. Lek. – 2003. – № 49 (10). – P. 802–807.

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DINAMICS OF BLOOD PRESSURE AND HEART RATE VARIABILITY PARAMETERS DURING BIOFEEDBACK IN LOOP OF HEART RATE VARIABILITY AND PACED BREATHING IN PATIENTS WITH DIFFICULT-TO-CONTROL ARTERIAL HYPERTENSION ON THE BACKGROUND OF DRUG

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60 patients with difficult-to-control arterial hypertension (DTCAH) were examined (average age is 59.0 ± 9.4 years). The changes in blood pressure (BP) and parameters of heart rate variability (HRV) during biofeedback sessions (BFB) in loop of paced breathing (PB) in patients with DTCAH on the background of standard drug therapy were assessed. It has been established that the systematic sessions of BFB in loop of PB in patients with DTCAH allow to increase the total power of the HRV spectrum, VLF and HF, and also improve control of BP. BFB in loop of PB can be recommended as an adjunctive method to the standard drug therapy for patients with DTCAH.

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

ДИНАМІКА АРТЕРІАЛЬНОГО ТИСКУ ТА ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ ПРИ ПРОВЕДЕННІ СЕАНСІВ БІОЛОГІЧНОГО ЗВОРОТНЬОГО ЗВ'ЯЗКУ З КОНТУРОМ МЕТРОНОМІЗІРОВАННОГО ДИХАННЯ У ХВОРИХ НА ВАЖКОКОНТРОЛЬОВАНУ АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ НА ТЛІ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ

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Обстежено 60 пацієнтів з важкоконтрольованою артеріальною гіпертензією (ВАГ) (середній вік 59,0 ± 9,4 років). Були оцінені зміни артеріального тиску (АТ) і параметрів варіабельності серцевого ритму (ВСР) при проведенні сеансів біологічного зворотного зв'язку (БЗЗ) з контуром метрономізірованного дихання (МД) у пацієнтів з ВАГ на тлі стандартної медикаментозної терапії. Встановлено, що систематичне проведення сеансів БЗЗ в контурі МД у пацієнтів з ВАГ дозволяє збільшити загальну потужність спектра ВСР, показників VLF і HF, а також покращує контроль АТ. Сеанси БЗЗ в контурі МД можуть бути рекомендовані в якості доповнення до стандартної медикаментозної терапії пацієнтам з ВАГ.

КЛЮЧОВІ СЛОВА: біологічний зворотний зв'язок, варіабельність серцевого ритму, важкоконтрольована артеріальна гіпертензія

ДИНАМИКА АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И ПАРАМЕТРОВ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА ПРИ ПРОВЕДЕНИИ СЕАНСОВ БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ С КОНТУРОМ МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ У ПАЦИЕНТОВ С ТРУДНОКОНТРОЛИРУЕМОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ НА ФОНЕ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ

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Обследовано 60 пациентов с трудноконтролируемой артериальной гипертензией (ТАГ) (средний возраст 59,0 ± 9,4 лет). Были оценены изменения артериального давления (АД) и параметров вариабельности сердечного ритма (ВСР) при проведении сеансов биологической обратной связи (БОС) с контуром метрономизированного дыхания (МД) у пациентов с ТАГ на фоне стандартной медикаментозной терапии. Установлено, что систематическое проведение сеансов БОС в контуре МД

у пациентов с ТАГ позволяет увеличить общую мощность спектра ВСР, показателей VLF и HF, а также улучшает контроль АД. Сеансы БОС в контуре МД могут быть рекомендованы в качестве дополнения к стандартной медикаментозной терапии пациентам с ТАГ.

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

INTRODUCTION

The inability to achieve the target level of blood pressure (BP) using three- and more-component drug therapy characterizes the difficult-to-control arterial hypertension (DTCAH). The prevalence of DTCAH in the population of people with arterial hypertension (AH) is from 15 to 30 % [1]. And the incidence of true refractory hypertension reaches 30 % of the total number of patients with DTCAH [2]. An insufficient effect of drug therapy is a prerequisite for finding additional, non-pharmacological methods of treatment. One of such methods is biofeedback (BFB) in loop of heart rate variability and paced breathing (PB).

Data from clinical trials demonstrate the efficacy of BFB in loop of heart rate variability (HRV) and PB for the treatment of patients with AH [3]. Systematic sessions of BFB in loop of HRV and PB affect the balance of the sympathetic and parasympathetic components of the autonomic nervous system [4]. Accordingly, the method influences BP and helps in achieving its control. However, in patients with DTCAH, the effectiveness of the method was not studied. It seems interesting to assess the response of BP and HRV parameters in patients with DTCAH on the background of drug support.

OBJECTIVE

Assessment of changes in BP and parameters of HRV during sessions of BFB in loop of HRV and PB in patients with DTCAH on the background of standard drug therapy.

MATERIALS AND METHODS

On the clinical base of the Kharkov city outpatient clinic № 24 and the State Institution «Kharkov Clinical Hospital for Railway Transport № 1» 60 patients with DTCAH were examined. The study involved 32 men and 28 women. Average age $59 \pm 9{,}4$ years. All patients participating in the study were randomly divided into two subgroups: BFB group with PB (33 patients) – main subgroup, comparison subgroup (27 patients).

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.

BP was measured by the Korotkov method with the tonometer Little doctor LD-91 in the sitting position after 15-minute rest.

The BFB was held in a sitting position after a 15-minute rest using a computer system CardioLab 2009 («HAI-Medica», Ukraine) with the «Biofeedback» module. The calculation of HRV parameters was carried out in real time within the 7-minute session.

The following parameters of HRV were determined in all subjects in 5-minute intervals to assess the state of regulatory systems [5]:

- TP – total power of the spectrum, a measure of the power of the effects of neurohumoral reactions (ms2);
- VLF – the power of the very low-frequency spectrum is associated with thermoregulation, renin-angiotensin system and sympathetic nervous system (ms2);
- LF – the power of the low-frequency spectrum is associated mainly with the sympathetic and partially parasympathetic links of regulation (ms2);
- HF – the power of the high-frequency domain of the spectrum is associated mainly with the parasympathetic regulating unit (ms2).

Accordingly with the purpose of the study, all patients were divided into two subgroups: basic (with BFB and PB) and a subgroup of comparison. For patients in the main subgroup, the breathing rate was set by the Biofeedback program module under the control of HRV parameters using the algorithm for finding the

optimal frequency of PB at the start with free breathing, while for patients of the comparison subgroup BFB sessions were simulated with respiratory rate equal to the free breathing frequency.

All patients received the same therapy in accordance with the recommendations on the prevention and treatment of AH of the Ukrainian and European associations of cardiologists [6]. Given the severity of hypertension, the presence of target organ damage and concomitant pathology, the following combinations of antihypertensive drugs were prescribed:

– Angiotensin-converting enzyme (ACE) inhibitor / renin-angiotensin-aldosterone blocker (RAAB) + calcium channel blocker (CCB) + diuretic.

– ACE inhibitor / blocker RAAB + CCB + diuretic + mineralocorticoid antagonist.

– Beta-adrenoblockers + ACE inhibitor / blocker RAAB + CCB + diuretic.

– ACE inhibitor / blocker RAAB + CCB + diuretic + antihypertensive drug with central action.

Statistical analysis was performed by using Microsoft Excel. In the table were recorded average values (M) and standard deviations (sd) of TP, VLF, LF, HF in patients with BFB in loop of heart rate variability and PB and in patients of comparison subgroup. The significance of differences of each of the indexes was determined by using the Student's t-test for unrelated samples.

RESULTS AND DISCUSSION

Changes in BP in patients with DTCAH in the subgroup with BFB in loop of PB and in the comparison subgroup are presented in Table 1.

Table 1

Changes in blood pressure in subgroups of patients with DTCAH during treatment (M ± sd, mm Hg)

BP indexes	Subgroups of patients							
	Main subgroup				Comparison subgroup			
	Phases of research							
	Before treatment	3 month	6 month	1 year	Before treatment	3 month	6 month	1 year
SBP (M ± sd, mm Hg)	181 ± 20,8*	176 ± 15,7*	155 ± 10,7	149 ± 6,2	180 ± 18,9	179 ± 21,5**	168 ± 17,2**	157 ± 7,9
DBP (M ± sd, mm Hg)	101 ± 12,2	95 ± 8,5#	92 ± 6,9#	88 ± 3,1	102 ± 13,2	96 ± 8,2	94 ± 7,4	95 ± 4,9

*Note: * – P < 0.05 in the series against the initial values; ** – P < 0.05 between series at the current stage; # – P < 0.05 in the series against the previous stage.*

Antihypertensive therapy in combination with BFB in loop of PB showed more significant decrease in BP in patients with DTCAH than in patients with BFB without PB. After a three-month treatment in patients of subgroups with BFB in loop of PB SBP decreased by 1.02 times, DBP - by 1.06 times. At the stage of half-yearly treatment the dynamics of BP was looked as follows: SBP decreased by 1.2 times, DBP – by 1.1 times. The results of one-year follow-up showed that SBP decreased by 1.2 times, DBP – by 1.14 times.

After a three-month stage of therapy the SBP in the comparison group decreased by 1.005 times, DBP – by 1.06 times. After half a year the SBP decreased by 1.07 times, DBP - by 1.08 times. At the annual stage SBP decreased by 1.1 times, DBP – by 1.07 times.

Table 2 shows the parameters of HRV in the subgroup of patients with BFB in loop of PB and in the comparison subgroup.

Table 2

Change in HRV parameters in subgroups of patients with BFB in loop of PB and in the comparison subgroup (M ± sd, ms2)

HRV indexes	Subgroups of patients							
	Main subgroup				Comparison subgroup			
	Phases of research							
	Before treatment	3 month	6 month	1 year	Before treatment	3 month	6 month	1 year
TP	1632 ± 1589	1853 ± 1736	1945 ± 1583	1973 ± 1496	1535 ± 1383	1503 ± 1175***	1426 ± 1327***	1497 ± 1425***
VLF	630 ± 838	783 ± 954**	963 ± 825**	836 ± 793**	572 ± 521	528 ± 517#	583 ± 536#	595 ± 427
LF	637 ± 757	698 ± 730	665 ± 835	648 ± 698	560 ± 867}	538 ± 624}	603 ± 674	627 ± 526
HF	335 ± 446*	472 ± 528*	438 ± 516	416 ± 549	357 ± 375	372 ± 493	324 ± 295	363 ± 305

*Note: * – P < 0.01 in the series against the initial values;} – P < 0.01 between series at the current stage; ** – P < 0.05 in the series against the initial values; *** – P < 0.05 between series at the current stage; # – P < 0.05 in the series against the previous stage.*

The baseline values of TP and VLF in the subgroup of patients with BFB and patients from comparison subgroup were almost identical (P < 0.05). Starting from the three-month stage BFB in loop of PB showed a positive effect on the HRV parameters, their more significant increase was observed with further preservation of the trend, while in the comparison subgroup they did not change during the entire monitoring period.

The initial level of HF in the compare subgroups was comparable (P < 0.05). BFB in loop of PB provided an increase in the indicator during monitoring period, whereas in the comparison subgroup it did not change significantly. The LF value remained almost the same in both subgroups (P < 0.05).

Comparison of BP and HRV parameters in patients with DTCAH in the main subgroup showed their synchronous positive dynamics, whereas in the comparison subgroup there were no significant changes.

The obtained results indicate that addition of drug therapy with BFB in loop of HRV and PB allows achieving better BP control in patients with DTCAH, which corresponds to the data in patients with controlled hypertension [3, 4]. There are no publications on the effectiveness of the use of BFB in loop of HRV and PB in patients with DTCAH in literature.

The results of the study indicate that BFB in loop of HRV and PB can be used in patients with DTCAH to improve the quality of its control, which makes it possible to recommend the method as a component of non-drug treatment for patients with DTCAH.

CONCLUSIONS

1. Systematic sessions of BFB in loop of PB in patients with DTCAH allow increasing the overall power of the spectrum of HRV, including its components – VLF and HF, and also improve control of BP, while one drug therapy does not significantly effect on them.
2. BFB sessions in loop of PB can be recommended as a supplement to standard medical therapy for patients with DTCAH.

The efficacy of BFB in loop of HRV and PB in patients with DTCAH and controlled hypertension is the interest to compare in the future.

REFERENCES

1. Achelrod D. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations / D. Achelrod, U. Wenzel, S. Frey. // Am J Hypertens. – 2015. – № 28. – p. 355–361.
2. Comparative epidemiology of resistant hypertension in chronic kidney disease and the general hypertensive population / [P. A. Sarafidis, P. I. Georgianos, P. E. Zebekakis, et al.]. // Semin Nephrol. – 2014. – № 34. – p. 483–491.

3. Belal S. A. S Vliyanie seansov biologicheskoy obratnoy svyazi s zamknu-tyim konturom variabelnosti serdechnogo ritma i metronomizirovannogo dyihaniya na kontrol sistolicheskogo arterialnogo davleniya na fone standartnoy medikamentoznoy terapii u patsientov s arterialnoy gipertenziey / S. A. S. Belal, N. A. Vodyanitskaya, N. I. Yabluchanskiy. // Visnik Harkivskogo natsionalnogo universitetu im. V. N. Karazina, seriya: «Meditsina». – 2015. – № 29. – S. 11–21.
4. Otsenka effektivnosti primeneniya biologicheskoy obrat-noy svyazi v zamknutom konture variabelnosti serdechnogo ritma i metro-nomizirovannogo dyihaniya u patsientov s arterialnoy gipertenziey / A. L.Kulik, E. Yu. Shmidt, A. V. Martyinenko, N. I. Yabluchanskiy. // Visnik Harkivskogo natsionalnogo universitetu imeni V. N. Karazina, seriya: «Meditsina». – 2011. – № 22. – S. 29–37.
5. Yabluchanskiy N. I. Variabelnost serdechnogo ritma v pomosch prakticheskomu vrachu / N. I. Yabluchanskiy A. V.MartInenko // – X.: Dlya nastoyaschih vrachey, 2010. – 131 s.
6. 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.

Clinical case

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LATE COMPLICATIONS AFTER THERAPY IN PATIENT WITH HODGKIN'S LYMPHOMA

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During the past five decades, dramatic progress has been made in the development of curative therapy for hematologic malignancies, including Hodgkin's Lymphoma (HL). The therapy responsible for this survival can also produce adverse long-term health-related outcomes, referred to as «late effects», which manifest months to years after completion of cancer treatment.

The purpose of this report is to pay attention to the problem of late complications, which develop in distant period after combined therapy of HL on example of illustrative clinical case.

KEY WORDS: Hodgkin's Lymphoma, treatment complications, pericardial effusion, heart failure, pneumofibrosis, chronic kidney disease

ПІЗНІ УСКЛАДНЕННЯ ТЕРАПІЇ У ПАЦІЄНТКИ З ЛІМФОМОЮ ХОДЖКІНА

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Протягом останніх п'ятдесяти років медицина досягла значних успіхів в лікуванні онкогематологічних захворювань. Терапія, завдяки якій були досягнуті ці результати, згодом може призводити до ускладнень, званими «пізніми ефектами». Останні можуть маніфестувати від декількох місяців до декількох років після завершення лікування лімфоми.

Мета цієї статті - на наочному прикладі клінічного випадку звернути увагу на проблему пізніх ускладнень, які розвиваються в віддаленому періоді після комбінованої терапії лімфоми Ходжкіна.

КЛЮЧОВІ СЛОВА: лімфома Ходжкіна, ускладнення терапії, перикардіальний випіт, серцева недостатність, пневмофіброз, хронічна хвороба нирок

ПОЗДНИЕ ОСЛОЖНЕНИЯ ТЕРАПИИ У ПАЦИЕНТКИ С ЛИМФОМОЙ ХОДЖКИНА

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В течение последних пятидесяти лет медицина добилась значительных успехов в лечении онкогематологических заболеваний. Терапия, благодаря которой были достигнуты эти результаты, впоследствии может приводить к осложнениям, называемым «поздними эффектами». Последние могут манифестировать от нескольких месяцев до нескольких лет после завершения лечения лимфомы.

Цель настоящей статьи – на примере показательного клинического случая обратить внимание на проблему поздних осложнений, которые развиваются в отдаленном периоде после комбинированной терапии лимфомы Ходжкина.

КЛЮЧЕВЫЕ СЛОВА: лимфома Ходжкина, осложнения терапии, перикардиальный выпот, сердечная недостаточность, пневмофиброз, хроническая болезнь почек

INTRODUCTION

With advances in therapy, HL has become highly curable, with survival rates approaching 95 % for patients with early-stage disease and 75 % for those with advanced disease [1–3]. Unfortunately, the improved prognosis of HL has been accompanied by elevated risks of second malignancies (leukemia, lung, stomach, breast, bone, colorectal cancers, etc.), cardiac disease (coronary artery disease, conduction abnormalities, valvular disease, pericardial disease), pulmonary dysfunction, infections, endocrinopathy.

Researches have demonstrated that late effects contribute to a high burden of morbidity, including the following: 60 % to more than 90 % develop one or more chronic health conditions; 20 % to 80 % experience severe or life-threatening complications. Investigations demonstrated that the elevated risk of morbidity and mortality among aging survivors in the cohort increases beyond the fourth decade of life. By age 50 years, the cumulative incidence of a self-reported severe, disabling, life-threatening, or fatal health condition was 53.6 % among survivors, compared with 19.8 % among a sibling control group. Among survivors who reached age 35 years without a previous severe, disabling, life-threatening health condition, 25.9 % experienced a new severe to fatal health condition within 10 years, compared with 6.0 % of healthy siblings [4]. The presence of serious, disabling, and life-threatening chronic health conditions adversely affects the health status of aging survivors, with the greatest impact on functional impairment and activity limitations. Female survivors demonstrate a steeper trajectory of age-dependent decline in health status compared with male survivors [5]. The even higher prevalence of late complications among clinically ascertained cohorts is related to the subclinical and undiagnosed conditions detected by screening and surveillance measures [6].

CLINICAL CASE

Our patient was 37 year old well-groomed and good mood female. On admission patient suffered from dyspnea during exertion (especially when going uphill or upstairs), even ordinary physical activity provoked breathlessness, ankles edema in the evening, face and eyelid puffiness in the morning, palpitations, tendency to hypotension (85/55 mm Hg).

In 1993, when she was 15 years old, Hodgkin's Lymphoma of mandibular, cervical, intrathoracic lymph nodes had been diagnosed. The combination therapy had been carried out, but particular regimens and medicines patient currently do not remember. Bilateral cervical, supra-, infraclavicular, axillar as well as mediastinal regions radiotherapy had been performed. Since 1996 remission occurs, relapses did not observe.

During last three years dyspnea and ankle swelling bother the patient. She was surveyed in cardiologic center and for the first time was established diagnosis «Mild pericardial effusion. Chronic congestive heart failure II FC NYHA». It was prescribed: salt restriction in diet (< 3 g per day), torasemide 5 mg in the morning and ivabradine 7.5 mg. Symptoms decreased (but not completely ceased), exercise tolerance slightly improved. During the last month dyspnea and exercise intolerance were exacerbated, even ordinary physical activity and walking ground level less then 500 m led to breathlessness. Also palpitations had developed. Due to symptoms deterioration, patient had been referred to cardiologic department.

Examination revealed following changes. The general condition of the patient was satisfactory, she was not in distress. Not obese. On the lower part of the neck to the left presented small scar due to lymph node biopsy in 1995. Mild ankle edema was detected. All groups of lymph nodes were not palpable, in the axillary region to the right palpated dense scar tissue (painless, possibly post beam therapy). No visible enlargement of thyroid gland, but it was palpated, size was slightly increased, painless, had smooth surface, homogeneous structure, nodules were not detected. JVP 4.7 cm was above the sternal angle. Lungs to auscultation vesicular breath sounds. Apex beat localized in the 5^{th} intercostal space, diffuse and diminished force. Heart to auscultation: S1 and S2 were soft, systolic murmur heard over mitral valve, pericardial friction rub along the left sternal border. Abdomen was soft and nontender. Liver: percussion – 13/12/9 cm, palpated 4 cm lower than right costal arch, nontender and soft, and had smooth surface. Spleen: percussion – 10/15 cm, palpated 6 cm lower than left costal arch, tenderless, had elastic consistency and smooth surface. The

kidneys were not palpable. Stool and diuresis were unremarkable.

Clinical data revealed following findings. Complete blood count and urine analysis were unremarkable. Plasma glucose, liver function tests, ESR, C-RP, ASL-O, RF, thyroid hormones fell in reference range. Kidney function was decreased: serum creatinine 97 mkmol/L, eGFR = 60 ml/min/1.73m^2 (by MDRD formula). Also it was occurred diuretic induced iatrogenic hypokalemia (3.2 mmol/L). ECG revealed sinus tachycardia (110 bpm), electrical alternant, complete RBBB, left ventricle overload, PR-segment depression in II, III, AVF, PR-segment elevation in AVR, ST-segment depression in I, II, III, AVF, V1-V6, ST-segment elevation in AVR, V1. On Holter ECG monitoring was not detect rhythm abnormalities. Echocardiography found mild pericardial effusion (echo-free pericardial space up to 7 mm), aortic fibrosis myocardial contractility was preserved EF 75 %, but heart chambers were diminished in size and cardiac output was only 47 ml. Chest CT scan detected lung roots fibrosis and cardiomegaly with mild hydropericardium (maximal fluid thickness 14 mm), minimal upper mediastinal lymphadenopathy with no reliable progression by comparison with 2008 year. Abdomen ultrasound detected hepatosplenomegaly (liver: right lobe 15,5 cm, left lobe 8 cm; spleen: 7.5 cm/15 cm), diminished left kidney about two times of normal (hypoplasia? or drug nephrotoxicity?), urolithiasis.

Based on complaints, patient's past medical history, and physical examination final diagnosis had been established:

Main disease. Hodgkin's Lymphoma, remission

Complications. Late Hodgkin's lymphoma therapy complications: chronic mild pericardial effusion, diffuse cardiosclerosis following aseptic myocarditis, aortic valve sclerosis, sinus tachycardia, right bundle branch block, chronic congestive heart failure with preserved EF (75 %), II FC NYHA, hypoplasia? (drug induced atrophy?) of the left kidney, CKD II stage, hepatomegaly with splenomegaly, diffuse nodular non-toxic goiter.

Management of the patient is directed to the improvement of patient's symptoms and quality of life. It was recommended follow the diet low sodium and rich in potassium. For rate control it was prescribed ivabradine 7.5 mg bid. To prevent edema toracemide 5 mg was recommended. For hypokalemia correction potassium chloride 600 mg bid under control of serum potassium was prescribed. To prevent heart failure progression low doses of ACE-inhibitor ramipril 1.25 mg was recommended. For pericardial effusion was recommended low doses of NSAIDs, aspirin 500 mg under gastroprotection by PPI inhibitors pantoprazole 40 mg.

Outcome. Despite of therapy, pericardial effusion persist by control echocardiography data, amount of pericardial fluid was not change. Symptoms ceased, physical tolerance slightly increased, but lower extremities edema and morning eyelid puffiness was observed.

CONCLUSIONS

Patients, who have been treated for Hodgkin's disease, despite being cured of their malignancy, may develop iatrogenic complications that lead to premature mortality. A substantial excess risk of mortality may be attributable to second cancers and cardiac diseases. Multitude of patients has been treated with anthracyclines or chest radiation, both of which may cause cardiovascular and kidney damage. The frequency of long-term complications in patients treated for Hodgkin's disease makes continued follow-up an important part of their care. This follow-up should include efforts to prevent morbidity and mortality by early diagnosis and attention to risk factors. Future treatment regimens for Hodgkin's disease should be designed attempting to minimize these complications.

REFERENCES

1. Long-Term Cause-Specific Mortality of Patients Treated for Hodgkin's Disease / [B. M. Aleman, A. W. van den Belt-Dusebout, W. J. Klokman, et al.] // Journal of Clinical Oncology. – 2003. – P. 3431–3439.

2. Late Effects of Treatment for Childhood Cancer (PDQ®): Treatment - Health Professional Information [NCI] [electronic resource] // HealthLinkBC. – 2016. – Access to the source: https://www.healthlinkbc.ca/health-topics/ncicdr0000343584.
3. Hodgkin disease survival in Europe and the U.S.: prognostic significance of morphologic groups / [C. Allemani, M. Sant, R. De Angelis, et al.] // Cancer. – 2006. – № 107. – P. 352–360.
4. Aging and Risk of Severe, Disabling, Life-Threatening, and Fatal Events in the Childhood Cancer Survivor Study / [G. T. Armstrong, T. Kawashima, W. Leisenring, et al.] // Journal of Clinical Oncology. – 2014. – № 32 (12). – P 1218–1227.
5. Survivors of Childhood Cancer in the United States: Prevalence and Burden of Morbidity / [S. M. Phillips, L. S. Padgett, W. M. Leisenring, et al.] // Cancer Epidemiol Biomarkers Prev. – 2015. – № 24 (4). – P. 653–663.
6. Clinical ascertainment of health outcomes among adults treated for childhood cancer / [M. M. Hudson, K. K. Ness, J. G. Gurney, et al.] // JAMA. – 2013. – № 309 (22). – P. 2371–2381.

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A CLINICAL CASE OF WEBER-CHRISTIAN DISEASE

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A clinical case of elderly female patient diagnosed with Weber-Christian disease developed on the background of long standing chronic autoimmune thyroiditis with impaired function of the thyroid gland (hypothyroidism) and unstable hormonal status, after surgery (hysterectomy, oophorectomy).

KEY WORDS: Panniculitis, Weber-Christian Disease, autoimmune thyroiditis

КЛІНІЧНИЙ ВИПАДОК ХВОРОБИ ВЕБЕРА-КРІСЧЕНА

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Клінічний випадок хвороби Вебера-Крісчен у пацієнтки похилого віку, яка розвинулася на фоні тривало протікаючого хронічного автоімунного тиреоїдиту з порушеною функцією щитовидної залози (гіпотиреоз) та нестабільного гормонального статусу після хірургічного втручання (гістеректомія, оваріектомія).

КЛЮЧОВІ СЛОВА: панікуліт, хвороба Вебера-Крісчена, автоімунний тиреоїдит

КЛИНИЧЕСКИЙ СЛУЧАЙ БОЛЕЗНИ ВЕБЕРА-КРИСЧЕНА

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Клинический случай болезни Вебера-Крисчена у пациентки пожилого возраста, которая развилась на фоне длительно протекающего хронического аутоимунного тиреоидита с нарушенной функцией щитовидной железы (гипотиреоз) и нестабильного гормонального статуса после хирургического вмешательства (гистеректомия, овариектомия).

КЛЮЧЕВЫЕ СЛОВА: панникулит, болезнь Вебера-Крисчена, аутоимунный тиреоидит

INTRODUCTION

Weber-Christian disease (idiopathic lobular nonsuppurative panniculitis) is a rare systemic disease of the connective tissue from group of panniculitis. The incidence and prevalence of Weber-Christian disease is unknown. Less than 200 cases have been reported so far [1]. Currently there is no single concept of the etiology and pathogenesis of this disease. Presumably immune-pathological nature of the disease plays a role with such provoking factors as injury, surgery, disorders of fat metabolism and the endocrine system, liver and pancreas [1–3]. Weber-Christian disease (WCD) is characterized by the acute (subacute) appearance of erythematous, edematous, and tender subcutaneous nodules 2 cm in diameter and more in the upper and lower extremities, trunk and face. Individual nodules usually resolve over a 2-week period, leaving an atrophic depressed scar.

Depending on the form of the nodules there are 3 main clinical forms of WCD [4]:

1. Nodular – lesions are isolated from each other, do not coalesce, clearly demarcated from the surrounding tissue with normal skin color to bright pink color;
2. Plaque – nodules are merged in a dense lumpy conglomerate, color over it varies from pink to bluish-purple;
3. Infiltrative – fluctuations in the area of separate lesions or conglomerates with red, purple or bluish-purple color.

In addition to specific changes in the skin and subcutaneous fat, Weber-Christian disease

appear next to non-specific symptoms, such as myalgia, arthralgia, high or low-grade fever, weight loss, which often complicates the diagnostics of this disease and increases the rate of referral frequency to various specialists [5].

Laboratory data of patients with WCD are non-specific and include increased ESR, leukocytosis or leucopenia and eosinophilia. Biopsy of lesions usually reveal presence of edema, foci of necrosis of fat lobules, cell infiltration with lymphocytes, plasma cells, histyocytes playing a role in histological confirmation of the diagnosis[4].

There is no specific treatment for Weber-Christian disease. Therapeutic responses have been reported with the use of corticosteroids, hydroxychloroquin, azathioprine, thalidomide, cyclophosphamide, tetracycline, cyclosporin and mycophenolate mofetil [4, 6–7].

Prognosis of WCD widely varies. Significant morbidity and mortality may occur in patients with inflammation involving visceral organs and poor response to therapy.

OUR CASE

Female patient of 57 years-old presented with complaints on a burning sensation and tightness of the skin in the area of the anterior abdominal wall, loin, hips; pain in the cervical, thoracic, lumbar regions of spine, joints of wrists, feet, knees with the mechanical rhythm of pain and morning stiffness for about 15 minutes, «crepitus» in the joints during movement and restriction of its motion; torso muscle pain. Also complains were of recurrent headaches of diffuse nature, dizziness, fatigue, general weakness, periodical chest pain without irradiation provoked by stress, relieved in rest; hearing loss. Patient was concerned about progressive memory loss, periodical chills, feeling of a lump in the throat, difficulty in swallowing.

Anamnesis of the disease. From early childhood, the patient had acquired skin defects (extensive scarring), presumably due to past infectious lesions of the skin in the early neonatal period (in the age of 4 days). However, in 2008 after surgery for uterine leiomyoma, the patient began to notice the appearance of a feeling of skin tightness in the area of these lesions, muscle aches, joint pain, aching, diffuse abdominal pain, periodical increase of temperature up to 37, 2 C°. Patient didn't seek for medical care because of these complaints, considering these symptoms as signs of «violations of the thyroid gland function» (since 1987 had chronic autoimmune thyroiditis, hypothyroidism, takes L-thyroxine) and «hormonal changes» after the operation. Since 2012 the patient's condition began to deteriorate progressively – the feeling of skin tightness has intensified, appeared painful nodules with bluish-purple staining of the skin with fluctuation over it in the area of the front wall of the abdomen, loin, hips; memory worsened significantly, appeared pain in the area of thyroid gland projection, dizziness. The patient referred to the endocrinologist, neurologist, dermatologist and was sent for consultation to the genetic center, where Werner syndrome was suspected; but subsequently there were found no conclusive data indicating the presence of Werner syndrome due to the criteria by International Registry of Werner's syndrome group [8]. In 2013, she was consulted by rheumatologist and directed to the rheumatology department, where she was diagnosed with idiopathic recurrent lobular nonsuppurative panniculitis (Weber-Christian disease); she was treated with corticosteroids and NSAIDs with positive dynamics of her state – decreased temperature, diminished pain and skin changes. Subsequently, the patient is held annually examinations and treatment in a specialized rheumatological department.

Anamnesis of life. Patient is not working; denies smoking, alcohol abuse. She had surgical menopause since 2008 – hysterectomy, oophorectomy due to leiomyoma of uterus. According to the patient 30 years ago she was first diagnosed with chronic autoimmune thyroiditis, hypothyroidism; constantly takes L-thyroxin (75–100 mg). First was diagnosed with high blood pressure 7 years ago, constantly takes antihypertensive drugs (lisinopril). From postponed illnesses: chronic bilateral sensoneural hearing loss 3d–4th degree (since 2002); median tunnel syndrome of the left arm (surgical treatment in 2002, 2014); ischemic stroke in the basin of the left middle cerebral artery with right-sided hemiparesis (16.07.2015); encephalopathy of mixed origin (hypertensive, atherosclerotic, dyshormonal), retinal angiopathy of both eyes of hypertensive type, open-angle glaucoma of both eyes 1a degree (2016); right upper jaw granulomas in the area of 14, 16, 17 teeth (surgical treatment in 2016);

Objective examination. General condition of the patient is satisfactory, clear consciousness, posture is active. Patient is oriented in place, time, herself. Height – 162 cm, weight – 76 kg, BMI = 29 kg/m^2. Skin: pale with areas of vitiligo; slightly dry, skin turgor preserved; on the front of the abdominal wall – skin hypotrophy with elements of scarring and slight cyanosis; in the right thigh – skin scarring with purple-bluish coloration, slightly painful on palpation. Visible mucous membranes are clean, moist; subcutaneous adipose tissue is developed moderately, distributed symmetrically. Musculoskeletal system: the outline of small joints of the hands, wrist, knee, ankle, foot joints is smoothed. There are solitary Heberden's nodes in the distal interphalangeal joints (DIP) and Bouchard's nodes in the proximal interphalangeal joints (PIP) of the hands; in the 1st metatarsophalangeal joints (MTP) joints of the feet – signs of exostosis. On palpation joints are painless, with crepitus on motion. Thyroid gland is not enlarged. Lungs: resonance percussion sound on percussion, vesicular breathing over the lungs fields on auscultation, RR-19/'. Heart borders on percussion are extended to the left on 1 cm, heart tones on auscultation are rhythmic, clear with HR 72 bpm. BP *sin* 158/100 mm Hg, *dext* 160/102 mm Hg, radial pulse is synchronous, rhythmic at 72 bpm. Abdomen: abdomen is soft, 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.

The results of current patient's investigations: full blood count: leucocytosis: 9,5*10^9/L, increased ESR: 20 mm/h, eosinophilia: 7 %; urinalysis, fasting plasma glucose, lipid profile, thyroid function tests – all parameters within the normal range; electrolytes: decreased ionized Ca – 1,0mmol/l; serological tests: positive ANA (antinuclear antibodies), positive anti-dsDNA (anti-double stranded DNA) with titer of 40U/ml. Anti-ENA (anti-extractable nuclear antigen), anti-JO-1, Anti-chromatin, anti-Scl70, anti-centromere antibodies were negative.

X-ray of wrists: asymmetric narrowing of the interarticular space; subchondral sclerosis, presence of small (fine) sybchondral cysts, signs of osteoporosis, soft tissue enlargement; x-ray of left foot: asymmetric narrowing of the interarticular space; subhondral sclerosis, presence of small (fine) sybchondral cysts, osteophytes, deformity in the area of PIP, DIP joints; MRI of spine – polysegmental vertebral osteochondrosis, spondylarthritis, spondylosis, disc protrusions at the level L3–L4, L5–S1; densitometry of forearm – mineral density in distal region is decreased, osteopenia, T-score: – 1,8; densitometry of spine – mineral density of L1, L2, L3, L4 is decreased – significant osteopenia, total T score: – 2,4.

Ultrasonography of thyroid gland: total volume: 10 cm^3; isthmus: 6 cm^3; diffuse-focal pathological changes of thyroid gland.

ECG: sinus rhythm with HR – 74, horizontal position of electric axis of the heart, non-specific ST-T changes in left ventricular posterior wall; ECOCG: sclerotic changes in the walls of the aorta, signs of left ventricular hypertrophy.

Biopsy of skin: patient refused to do biopsy.

Diagnosis: Main: Reccurent lobular nonsuppurative panniculitis (Weber-Christian disease), chronic course, activity of 1-st., with primary subcutaneous fat tissue lesion (infiltrative form). Primary polyosteoarthritis with lesions of small joints of wrists, wrist, ankle, knee, small joints of the feet. Spondyloarthritis. Insufficiency of the joint function I degree, Ro I. Osteopenia.

Concomitant diagnosis: Chronic auto-immune thyroiditis, diffuse-nodular form. Hypothyroidism, severe form, compensatory stage. Osteochondrosis with a lesion of the lumbo-sacral spine. Polysegmetal unstable form. Instability of the vertebral-motor segments of L3–L4, L4–L5, L5–S1, herniated intervertebral disks of L4–L5, L5–S1. Arterial hypertension stage III (ischemic stroke 2015), grade 2. Retinal angiopathy of both eyes of hypertensive type, open-angle glaucoma of both eyes 1a degree. Ischemic heart disease. Atherosclerotic cardiosclerosis. CHF, stage IIa, with preserved left ventricular pump function (EF – 62 %), III FC (NYHA). CV Risk 4. Overweight (BMI – 29kg/m^2).

Recommendations and treatment. Recommendations were to maintain healthy lifestyle, decrease sodium intake, lipid lowering diet, aerobic non strenuous exercises. Recommended drugs were: hydroxychloroquine (plakvinil) 0.2 g 2 time per day for a long time; meloxicam 15 mg per day – 10 days, and in the subsequent course of no more than 10 days in the event of pain; glucosamine sulfate 1500 mg per day for 3 months, after 6 months a second

course may be given; osteogenon (combined formulation with calcium and phosphorus) 2 tab twice daily for 6 months under the control of serum calcium and phosphorus; pantoprazole, 40 mg once daily for 7 days; L-thyroxin 100 mg per day under control of thyroid hormones; bisoprolol 5 mg in the morning, lisinopril 10mg in the evening under blood pressure control; aspirin 75 mg once daily continuously. Also the patient was recommended to repeat densitometry after 6 months, autoantibodies after 3 months; repeat visit to rheumatologist, endocrinologist, neurologist after 3 months.

DISCUSSION

Weber-Christian disease in our patient developed on the background of long standing chronic autoimmune thyroiditis with impaired function of the thyroid gland (hypothyroidism). The hormonal status of the patient showed significant fluctuations over years despite of *thyroid* hormone *replacement therapy* (Figure 1, 2).

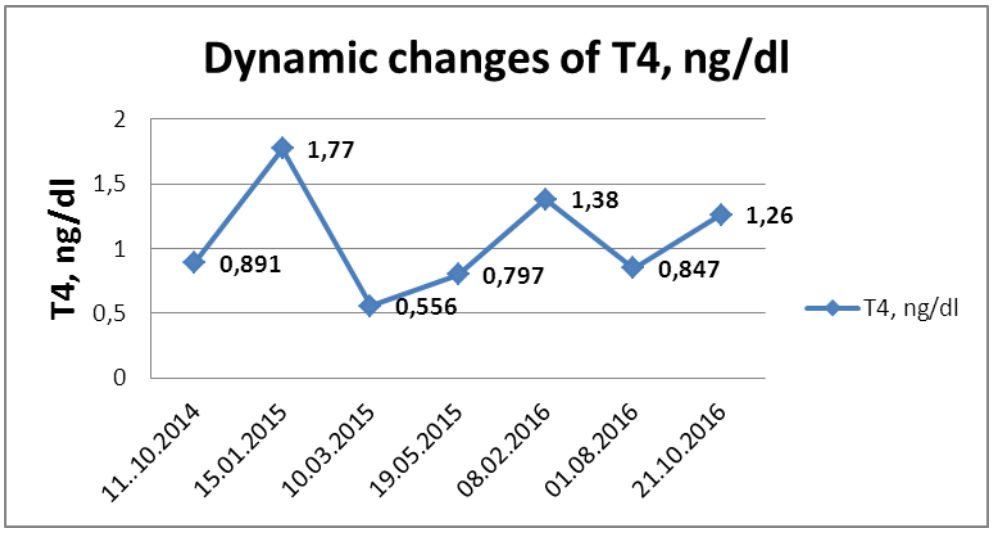

Fig. 1. Dynamic changes of T4 in period of 2014-2016 years; T4 – L-thyroxin, ng/dl.

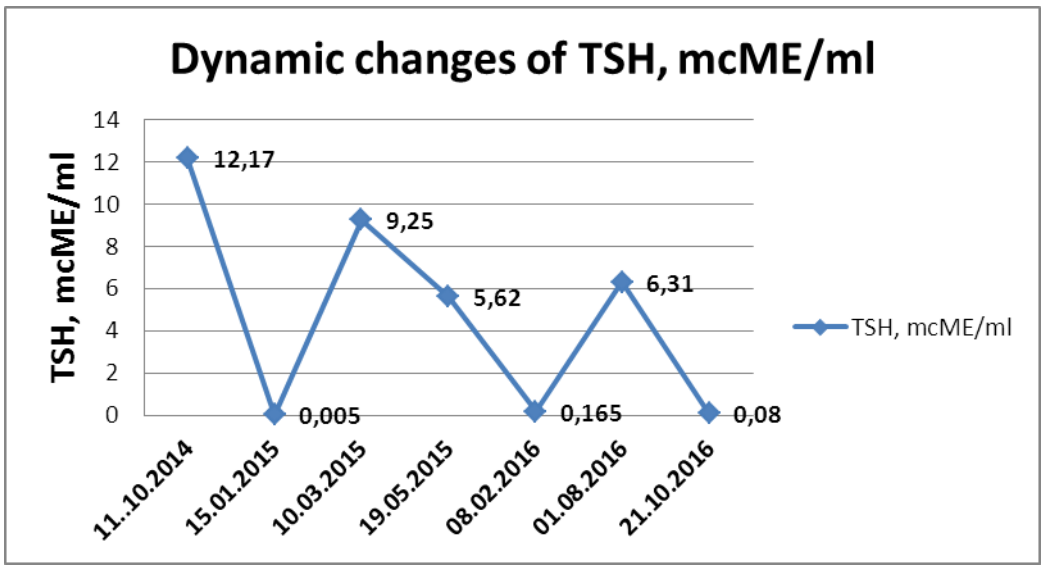

Fig. 2. Dynamic changes of TSH in period of 2014-2016 years; TSH-thyroid-stimulating hormone, mcME/ml.

Although the causes and pathogenesis of Weber-Christian disease are not yet established and are the subject of discussion, a number of studies demonstrate the existence of a linkage of WCD to autoimmune diseases. There are reported cases of Weber-Christian disease associated with autoimmune chronic hepatitis [8], glomerulonephritis [9], diabetes mellitus [8], rheumatologic diseases such as rheumatoid arthritis [7] and vasculitis [10], as well as an increase in antibody titers such as ANA [10–12], anti-dsDNA [8, 13], as well as in our patient, and also ACA [14, 15], which may indicate the participation of immune mechanisms in the development of this disease. Studies highlight surgical interventions, hypothermia, infections, endocrine diseases as possible risk factors in the development of WCD [1–3, 5, 16]. The clinical manifestations of Weber-Christian disease in our patient occurred after surgery (hysterectomy, oophorectomy), which was probably a trigger factor in this case.

Despite the fact that the patient refused to perform biopsy and histological data was not obtained, the clinical picture of the disease, compliance with the criteria of the Ukrainian association of rheumatologists [4], as well as the positive effect of treatment with corticosteroids and hydroxyquinolone allowed diagnosis of Weber-Christian disease in our patient.

CONCLUSIONS

Weber-Christian disease still remains a medical mystery with unknown causes and mechanisms of its occurrence. This clinical case is an observation that supports the immune theory of the development of this disease and is an illustration of the fact that the key factors for the early diagnosis of rare diseases such as WCD are a careful history taking, attentive and accurate approach to the patient, as well as a systematic analysis of laboratory and instrumental surveys.

REFERENCES

1. Dermatology / [Otto Braun-Falco, Gerd Plewig, Helmut H. Wolff, et al.] // Springer Science & Business Media. – 2013. – 1235 p.
2. Belov B. S. Pannikulity v praktike revmatologa / B. S. Belov, O. N. Egorova, S. G. Radenska-Lopovok // Nauchno-prakticheskaja revmatologija. – 2013. – № 51 (4). – p. 407– 415.
3. Eyal Muscal. Weber-Christian disease [electronic resource] / Eyal Muscal. – Access mode: http://emedicine.medscape.com/article/1008411-overview.
4. Nomenklatura, klasifikacija, kriterii diagnostiki ta programi likuvannja revmatichnih hvorob / Pod red. Kovalenko V. M., Shuba N. M. // Kiïv. – 2004. – p. 57–60.
5. Idiopaticheskij pannikulit Vebera-Krischena: klinicheskie aspekty / [O. N. Egorova, B. S. Belov, S. I. Gluhova, et al.] // Sovremennaja revmatologija. – 2016. – № 10 (1). – p. 15–20.
6. Sharma A. K. Idiopathic lobular panniculitis (Weber Christian disease): A case report / A. K. Sharma, P. R. Sharma // Kathmandu University Medical Journal. – 2006. – Vol. 4, № 2 (14). – p. 243–245.
7. A patient with Pfeifer-Weber-Christian Disease - Successful Therapy with Cyclosporin A: case report / [Georg Pongratz, Boris Ehrenstein, Wolfgang Hartung, et al.] // BMC Musculoskeletal Disorders. – 2010. – № 11 (18). – Special section p. 1.
8. International Registry of Werner Syndrome [electronic resource]. – Access mode: http://www.wernersyndrome.org/registry/diagnostic.html.
9. Allen-Mersh T. G. Weber-Christian panniculitis and auto-immune disease: a case report / T. G. Allen-Mersh // Journal of clinical pathology. – 1976. – № 29 (2). – p. 144–149.
10. Dupont A. G. Weber-Christian panniculitis with membranous glomerulonephritis / A. G. Dupont, D. L. Uerbeelen, R. O. Six // The American Journal of medicine. – 1983. – № 75 (3). – p. 527–528.
11. Pfeifer-Weber-Christian's panniculitis in an obese patient with antinuclear antibody-positive leukocytoclastic vasculitis / [G. Foccillo, R. Giunta, C. De Capite, et al.] // Ann Ital Med Int. – 2002. – № 17 (2). – p. 121–125.
12. Parahina T. V. Zahvorjuvannja vebera-krischena (opis klinichnogo vipadku) / T. V. Parahina, U. I. Prijmich // Bil'. Suglobi. Hrebet. – 2016. – № 3 (23). – p. 74–78.
13. Successful treatment of steroid-resistant Weber–Christian disease with biliary ductopenia using cyclosporin A / [M. Hinata, T. Someya, H. Yoshizaki, et al.] // Rheumatology (Oxford). – 2005. – № 44 (6). – p. °821–823.
14. Sluchaj bolezni Vebera – Krischena / [A. A. Spasskaja, E. M. Haritonova, M. M. Gorodeckij, et al.] // Therapia. – 2008. – № 11 (31). – p. 53–56.

15. Yilmaz M. Weber-Christian disease presenting with pancytopenia and anticardiolipin antibodies / M. Yilmaz // Gaziantep Tep Dergisi. – 2007. – p. 39–41.
16. Weber–Christian disease associated with lupus anticoagulant and anticardiolipin antibodies / [J. Jimenez-Mazuecos, M. Yebra-Bango, A. Sanchez-Ruiz, et al.] // Rheumatology. – 1999. – № 38 (8). – p. 796–797.

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ACUTE PERICARDITIS ON EXAMPLE OF ILLUSTRATIVE CLINICAL CASE

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Pericarditis is an important diagnosis to consider in a patient presenting with chest pain. This article describes the common features and management of pericarditis in the general practice setting on the example of clinical case. To the cardiologic department was admitted middle aged male. He complained of sharp retrosternal pain, and fever. The survey revealed distinctive features of pericarditis: pericardial friction rub on auscultation, diffuse PR segment depressions on ECG, pericardial effusion on echocardiography, but etiology was not elicit. Most cases are labeled as «idiopathic» because the traditional diagnostic approach often fails to identify the etiology. The presence of febrile fever and neutrophilic leukocytosis indicates that a bacterial etiology take place. Prompt antibacterial and anti-inflammatory treatment led to recovery of the patient. He was completely free of symptoms and had returned to his pre-morbid state.

KEY WORDS: acute pericarditis, treatment of acute pericarditis, clinical case

ПЕРЕБІГ ГОСТРОГО ПЕРИКАРДИТУ НА ПРИКЛАДІ ПОКАЗОВОГО КЛІНІЧНОГО ВИПАДКУ

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При обстеженні пацієнта з болями в грудній клітині, важливо мати на увазі, що біль може бути обумовлена ураженням перикарда. Дана стаття на прикладі клінічного випадку описує найбільш типові прояви перикардиту та його лікування. В кардіологічне відділення поступив чоловік середніх років зі скаргами на загрудинну біль, лихоманку. В ході обстеження були виявлені характерні для перикардиту дані: шум тертя перикарда, лейкоцитоз, типові зміни ЕКГ, такі як депресія сегмента PR, а також виявлено перикардіальний випіт при ехокардіографії, проте етіологія не була визначена. Нерідко традиційні діагностичні методи не здатні ідентифікувати етіологічний фактор, тому найчастіше встановлюється діагноз «ідіопатичний» перикардит. Наявність фебрильної лихоманки та лейкоцитозу вказує на те, що найімовірніше має місце бактеріальна етіологія. Відповідна антибактеріальна та протизапальна терапія призвела до поліпшення стану та одужанню пацієнта.

КЛЮЧОВІ СЛОВА: гострий перикардит, лікування гострого перикардиту, клінічний випадок

ТЕЧЕНИЕ ОСТРОГО ПЕРИКАРДИТА НА ПРИМЕРЕ ПОКАЗАТЕЛЬНОГО КЛИНИЧЕСКОГО СЛУЧАЯ

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При обследовании пациента с болями в грудной клетке, важно иметь в виду, что боль может быть обусловлена поражением перикарда. В данной статье на примере клинического случая описываются наиболее типичные проявления перикардита и его лечение. В кардиологическое отделение поступил мужчина средних лет с жалобами на загрудинные боли, лихорадку. В ходе обследования были выявлены характерные для перикардита данные: шум трения перикарда, лейкоцитоз, типичные изменения ЭКГ, такие как депрессия сегмента PR, а также выявлен перикардиальный выпот при эхокардиографии, однако этиология не была определена. Зачастую традиционные диагностические методы не способны идентифицировать этиологический фактор, поэтому чаще всего устанавливается диагноз «идиопатический» перикардит. Наличие лихорадки и нейтрофильного лейкоцитоза указывает

на то, что вероятнее всего имеет место бактериальная этиология. Соответствующая антибактериальная и противовоспалительная терапия привела к улучшению состояния и выздоровлению пациента.

КЛЮЧЕВЫЕ СЛОВА: острый перикардит, лечение острого перикардита, клинический случай

INTRODUCTION

Acute pericarditis is the inflammation of the pericardial sac caused by infectious or noninfectious noxa with the possible increased production of pericardial fluid as exudates and less than 4 weeks duration [1]. Pericarditis is the most common disease of the pericardium encountered in clinical practice. But epidemiologic data are lacking, likely because this condition is frequently in apparent clinically, despite its presence in numerous disorders. Acute pericarditis caused 0.20 % of all cardiovascular admissions. The clinical diagnosis can be made with two of the following criteria:

– Chest pain (> 85–90 % of cases);

– Pericardial friction rub (≤ 33 % of cases);

– (ECG) changes (up to 60 % of cases): new widespread ST elevation or PR depression;

– Pericardial effusion (up to 60 % of cases, generally mild).

Additional signs and symptoms may be present according to the underlying etiology or systemic disease (i.e. signs and symptoms of systemic infection such as fever and leukocytosis, or systemic inflammatory disease or cancer) [2].

A leading expert on the study of pericarditis David H. Spodick believes, that contemporary understanding of acute pericarditis rests on 3 main considerations: (1) pericarditis occurs in every category of disease, common and exotic (the spectrum is so broad that with every new case, the clinician should devise an appropriate differential diagnosis), (2) to avoid therapeutic mishaps, pericarditis must not be mistaken for other syndromes, and (3) the etiological and clinical spectra of acute pericarditis change frequently and some classic assumptions and descriptions, perpetuated in some publications, are outdated [3]. Following clinical case display diagnostics and management of the patient with acute pericarditis in clinical practice.

CLINICAL CASE

The patient was 46 year old unemployed male. On admission he complained of dull, aching pain in the retrosternal region with radiation to the cervical spine, shoulders, interscapular area, which became worse on inspiration and supine position. It was persistent and three weeks duration. Occasionally patient noted palpitations. Other symptoms included: weakness, fatigue, fever (up to 39,5°C), body weight about 2 kg.

Three weeks prior to presentation, patient had been exposed to cold, since that moment in patient developed low grade fever (up to 37,5°C) and pain in the heart region. Patient thought he had been caught the cold, and used NSAIDs to relief symptoms, however, symptoms were not reduced, and fever gradation increased up to 39,5°C. General practitioner had prescribed for patient Amoxicillin 1000 mg tid. Five days of treatment were not effective and patient had been referred to cardiologic department.

No relevant past medical and social history were detected.

On examination it was revealed middle aged good mood man, who was well developed and well nourished. His appearance was consistent with his stated age. Fever (39.5 C) and tachycardia (100 bpm) occurred. Skin and mucous membranes were pink and clear. Edema was absent. Lymph nodes were not palpable. Vesicular breath sounds of the lungs to auscultation. The point of apex beat was diffuse (3 cm in diameter), impulse was diminished force, unchanged location. S1 and S2 were soft; pericardial frictions rub, best heard along the left lower sternal border. Gastrointestinal and urinary systems examination was unremarkable.

Complete blood count revealed signs of inflammation: neutrophilic leukocytosis (WBC 13.9 109/L, neutrophils 12.5 109/L – 89.9 %), increased ESR 34 mm/h. Urine analysis fell in normal ranges. Liver function tests and kidney function were normal. Troponin and, thyroid tests fell in reference range. ASL-O and RF were negative. Level

of C-RP was increased. Blood culture and PCR serum viruses' identification were negative. ECG revealed sinus rhythm, 89 bpm, normal heart axis, and pericarditis signs: PR-segment depression in II, III, AVF, PR-segment elevation in AVR, flattened T waves in all leads. Echocardiography showed signs of mixed serous-fibrinous mild pericardial effusion: presence of echo-free pericardial space up to 10 mm and floating fibrin threads there. Abdomen ultrasound showed splenomegaly with diffuse changes of parenchyma, other organs were normal. Thyroid ultrasound was normal. Chest X-Ray revealed enlarged heart, but lungs were not changed. Chest CT-scan detected fluid in the pericardial sac with max thickness up to 20 mm.

The presence of high, spiking fevers and neutrophilic leukocytosis indicates a bacterial etiology, but obtained blood culture was negative. Therefore in this case took place bacterial unspecified etiology. Based upon complaints, patient's past medical history, physical examination, and workup data final diagnosis had been established.

Main disease: Acute bacterial unspecified etiology serofibrinous (seroplastic) pericarditis with small amount of effusion.

Complications: Inflammatory splenomegaly.

Patient received following treatment. Wide spectrum antibiotic therapy: IV ceftriaxone 1000 mg bid and IV levofloxacin 500 mg qd in the course of ten days. Antiinflammatory therapy: Ibuprofen 600 mg po qid, Methylprednisolone 32 mg po for fourteen days, followed by dose tapering 4 mg every 2 weeks, and Pantoprazole 40 mg po bid simultaneously for gastroprotection [4]. Because after ten day course of antibacterial therapy complete recovery was not achieved – temperature and lab tests (persisted neutrophilic leukocytosis, WBC 11.2 109/L and neutrophils 9.9 109/L – 87.8 %) were not normalized, antibiotic treatment changed to Azithromycin 500 qd po for 5 days [5]. Whereupon resolution occurred.

On the background of the therapy the patient's condition improved: symptoms abated, body temperature turned into normal: 36.6–36.90°C, lab tests (WBC, ESR) were normalized, echocardiogram control after the treatment revealed significant reduction of the pericardial effusion. Patient was discharged from the hospital. It was recommended observation of the cardiologist and continuing methylprednisolone tapering.

CONCLUSIONS

Clinical case displayed particular features of the acute pericarditis, diagnostic consideration, and treatment recommendations. Characteristic clinical findings in pericarditis include chest pain and pericardial frictions rub on auscultation of the left lower sternal border. Electrocardiography reveals diffuse PR depressions and diffuse flattened T wave. Echocardiography showed mild pericardial effusion. The treatment includes empiric antibiotic and antiinflammatory therapies. This patient had uncomplicated course of disease. And in this isolated case take place positive trend of illness against the background of the conservative therapy. But 15 % to 30 % of patients with acute pericarditis recurrence may develop. The risk of recurrence is higher for women and for patients who do not have a response to initial treatment with NSAIDs.

REFERENCES

1. Imazio M. Evaluation and management of pericarditis [Electronic resource] / Massimo Imazio // Expert Reviews Cardiovascular Therapy. – 2011. – URL: http://www.medscape.com/viewarticle/751203.
2. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC). // European Heart Journal. – 2015. – № 36. – P. 2921–2964.
3. Spodick D. H. Acute pericarditis: current concepts and practice / Spodick. // JAMA. – 2003. – № 289. – P. 1150–1153.
4. Lysenko N. V. Use nonsteroidal anti-inflammatory drugs in therapeutic practice / N. V. Lysenko, I. V. Soldatenko, A. Yu. Kartvelishvili. // The journal of V. N. Karazin Kharkiv national university, series «Medicine». – 2010. – № 20. – P. 114–125.

5. Abduieva F. M. Klinichna farmakolohiia: Pidruchnyk dlia studentiv i likariv. / F. M. Abduieva, O. Y. Bychkova, I. O. Bondarenko, etc. – Kharkiv: V. N. Karazin Kharkiv national university, – 2011. – 405 p.

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ATRIAL FIBRILLATION IN A YOUNG PATIENT WITH A MYOCARDIAL BRIDGE

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On the example of a clinical case of atrial fibrillation (AF) in a young patient with a myocardial bridge (MB) were considered anatomical and physiological features, diagnostics, differential diagnosis of AF, and the setting of a clinical diagnosis. Recommendations for the modification of the lifestyle, as well as the tactics of medication, are described.

KEY WORDS: atrial fibrillation, myocardial bridge, diagnosis, treatment

ФІБРИЛЯЦІЯ ПЕРЕДСЕРДЬ У ПАЦІЄНТА МОЛОДОГО ВІКУ З МІОКАРДІАЛЬНИМ МІСТКОМ

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На прикладі клінічного випадку фібриляції передсердь (ФП) у пацієнта молодого віку з міокардіальним містком (ММ) розглянуто: анатомо-фізіологічні особливості, діагностика, диференціальна діагностика ФП і постановка клінічного діагнозу. Описано рекомендації по модифікації способу життя, а також тактика медикаментозного лікування.

КЛЮЧОВІ СЛОВА: фібриляція передсердь, міокардіальний місток, діагностика, лікування

ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ У ПАЦИЕНТА МОЛОДОГО ВОЗРАСТА С МИОКАРДИАЛЬНЫМ МОСТИКОМ

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На примере клинического случая фибрилляции предсердий (ФП) у пациента молодого возраста с миокардиальным мостиком (ММ) рассмотрены: анатомо-физиологические особенности, диагностика, дифференциальная диагностика ФП и постановка клинического диагноза. Описаны рекомендации по модификации образа жизни, а также тактика медикаментозного лечения.

КЛЮЧЕВЫЕ СЛОВА: фибрилляция предсердий, миокардиальный мостик, диагностика, лечение

INTRODUCTION

AF is the most common supraventricular tachyarrhythmia, in which the presence of foci of uncoordinated electrical activity in the atria, as well as disruption of the sequence and pulse propagation through the myocardium lead to a decrease in the contractility of the heart [1].

AF is the most common form of heart rhythm disturbance. This type of arrhythmia occurs in 1–2 % of the entire adult population and predominates in older men. In young people under the age of 25 almost does not occur, with age, its frequency increases from 0.5 % at the age of 40–50 years and to 5–15 % in 80-year-olds [1–3].

Over the past two decades, there has been an increase in the prevalence of AF among the urban population 6-fold, and 3-fold – in the rural population. The appearance of AF increases the overall mortality among men by 50 %, and among women by 90 %, after excluding the influence of age and other factors [1, 4].

For the onset of AF, a trigger mechanism is necessary, and often this mechanism is the foci of automatism located near the pulmonary veins. Cardiovascular diseases (arterial

hypertension, ischemic heart disease, chronic heart failure, hypertrophic cardiomyopathy, etc. including MB) may precede AF and cause it to develop. These diseases lead to myocardial heterogeneity, violation of the electric pulse, dispersion of refractory periods, which causes the formation of the mechanism of re-entry and contribute to the preservation of AF [1–2]. There is also an idiopathic AF, the cause of which is not established [1].

OBJECTIVE

To show the features of the management of a young patient with AF in combination with the MB. MB is a congenital anomaly of the development of the coronary arteries, in which part of the artery passes in the thickness of the myocardium and can be squashed during its operation [5].

Types of bridges: superficial (short (3–5 mm), long (30–40 mm)) and deep (penetration thickness up to 1 cm) [6]. The incidence of MB can vary from 5 % to 87 %. MB, as a rule, benign pathology of vascular development, which in 0,5–4,9 % of cases is of clinical importance and can be the cause of angina, myocardial infarction, ventricular tachycardia, AF, and sudden death [7].

MATERIALS AND METHODS

Clinical case. A man is 26 years old, he complains of periodic interruptions in the work of the heart, palpitation without a clear connection with the provoking factor more often after playing sports; dizziness; general weakness. There are complaints from other bodies and systems.

Anamnesis of the disease. The first appearance of the AF was during the study in February 2013. The patient was hospitalized in the city clinical hospital № 27, the rhythm was restored by amiodarone. After that, he occasionally took metoprolol, while observing short-term episodes of uneven rhythm up to 10 seconds with physical activity. There was an episode of AF during the sport. Man was hospitalized with repeated paroxysm in the hospital, where the sinus rhythm was restored by amiodarone in 2015.

The next relapse of AF was after drinking alcohol in May 2016. The attack was stopped by amiodarone, the consultation of the cardiosurgeon-arrhythmologist was recommended. He was hospitalized in KhNION in May 2016, where on May 27, 2016 the patient underwent radiofrequency ablation (RFA) with the isolation of pulmonary veins, linear ablation on the roof of the LP.

The patient asked for a consultation at the Department of Internal Medicine of V. N. Karazin Kharkov National University with complaints about periodic interruptions in the work of the heart, palpitation without a clear connection with the provoking factor; dizziness; general weakness in 10 April 2017.

Anamnesis of life. Living conditions are satisfactory. He is working as a system administrator. In childhood, he notes varicella, colds. Chronic diseases are denied. Tuberculosis, viral hepatitis, diabetes, mental and venereal diseases are denied. Injuries and other operations are denied. The presence of AF in the mother. The allergic anamnesis is not burdened. Bad habits are not abusing alcohol and are not taking drugs.

Objective status. The general condition is relatively satisfactory, the consciousness is clear, the position is active. Asthenic physique, height – 192 cm, weight – 80 kg, BMI – 21.7 kg/m^2. Skin covers and visible mucous membranes are clean, pale pink, there is no cyanosis. Lymph nodes are not enlarged. Thyroid gland is not visually determined, clearly not palpable, is painless. Musculoskeletal system without features. Peripheral edema are absent.

Respiratory system: above the lungs percussionally pulmonary sound, vesicular breathing. The HDR is 23 beats per minute.

Cardiovascular system: the boundaries of relative cardiac dullness are not biased. Cardiac activity is rhythmic, tones are muffled, heart rate is 95 beats per minute, BP on both hands is 110/70 mm Hg

The abdomen is of regular shape, not enlarged. Superficial palpation is painless, the symptom of irritation of the peritoneum is negative. The liver at the edge of the costal arch is painless during the palpation, the edge is smooth. The spleen is not palpable. The symptom of «effleurage» is negative on both sides.

RESULTS AND DISCUSSION

Clinical blood test. (11.04.17) Hg – 142 g/l, RBC – 4.77* 10^{12}/l, WBC. – 4.1* 10^{9}/L, ESR – 6 mm/hour, LYMPH. – 20 %, MONO. – 3 %.

Clinical analysis of urine. (11.04.17) Specific weight-1020, protein is absent, glucose

is absent, WBC – 0 in sp., L – 2 in p., transitional epithelium is absent.

Biochemical analysis of blood (11.04.17) Total bilirubin – 5.7 mkmol/l, direct – 2.9 mkmol/l, indirect – 9 mkmol/l, AlAt – 31ed/l, AcAt – 37ed/l, creatinine – 110 mkmol/l, glucose – 4,1 mmol/l, TP – 0 unit.

Hormones of the thyroid gland (17.02.13) TTG – 2,1mkMed/ml, T4 St. – 16,8pmol/l.

Lipidogram (11.04.17): total blood cholesterol is 5.8 mmol/l, HDL is 1.61 mmol/L, LDL is 3.76 mmol/l, TG is 1 mmol/l, KA – 2.06

Coagulogram (11.04.17) fibrinogen is 2.66, fibrin is 12, prothromb. ind. – 82 %.

ECG: 18.04.17 – sinus rhythm, incomplete blockade of anterior branch of LNGG. HR of 83 beats/min. Normal position of electric axis of heart.

Echocardiography (14.04.17): Myocodal noncompactness at the top of the left ventricle, the chambers of the heart are not enlarged, violations of LV wall kinetics have not been revealed.

Multidector CT coronary artery angiography (04/04/2015). Left main coronary artery (LM): atherosclerotic plaques and visible narrowing of the lumen are not revealed. Left atrial descending artery (LAD): At the level of the middle and distal part, the artery is closely attached, and also passes through the myocardium of the left ventricle, at a shallow depth, for 65 mm (variant of the myocardial bridge). Left stroke artery (LSx): Relatively significant narrowing of the lumen of the artery was not detected. Intermediate branch of left coronary artery (RI): Contrasted enough, significant narrowing of the lumen is not determined.

Right Coronary Artery (RCA): Dominance of the right coronary artery. The artery and its branches are contrasted sufficiently without apparent constriction. There were no destructive changes in the bones at the investigated level. Thinning of a compact layer of the myocardium with a thickening of the noncompact layer in the region of the apex and posterior wall, in close proximity to the apex

Daily monitoring of ECG (11/04/2017): monitored ECG was carried out for 20 hours 57 minutes. The average heart rate in the daytime is 83 beats/min, the average during the night sleep is 70 beats / min. The variability of the rhythm is moderately reduced. A total of 1215 (max 212 from 21:00 to 22:00), 9 paired, 2 runs of unstable supraventricular tachycardia, parasystole-2, monomorphic were identified. Deviations of the ST segment are not fixed.

HRV: The total power of the HRV spectrum is low (TP: 340 ms2).

The level and ratio of autonomic influences in cardiac rhythm modulation (VLF: 178ms^2, LF: 95 ms^2, HF: 60 ms^2) indicate a predominance of humoral metabolic regulation.

Differential diagnosis of AF. The reasons for the development of AF in this patient may be several factors:

1) The presence of MB contributes to ischemic damage to the myocardium, which leads to its structural change and disruption of the normal structure of the tissue.

2) Noncompactness of the myocardium, which leads to inhomogeneity of the myocardium and impaired conduction of the pulse along it.

3) Sympathicotonia and regular physical activity can cause the formation of foci of abnormal electrical activity due to shortening of the action potential and refractory period.

4) Drinking alcohol leads to an increase in the tone of the sympathetic nervous system.

5) Burdened heredity – the presence of AF in the patient's mother could contribute to its occurrence in our patient.

In this way, it is not possible to single out one single cause of AF, and hence the patient's treatment should be comprehensive and directed to all causes of the onset of the disease.

CONCLUSIONS

Clinical diagnosis. Main: Myocardial bridge of the LAD. Persistent form of atrial fibrillation, tachysystolic form. Radiofrequency ablation of the arrhythmogenic focus (isolation of pulmonary veins, linear ablation on the roof of the LP in 2016). Frequent supraventricular extrasystolic arrhythmia. Running unstable supraventricular tachycardia. CH 0 tbsp.

Treatment plan:

1) Clinical follow-up at a cardiologist, neuropathologist, endocrinologist.

2) Control daily monitoring after 2 months.

3) Motor mode with moderate dynamic physical loads (increasing the walking distance to 30 km per week).

4) Medication:

- Bisoprolol 5 mg heart rate control with dose selection,

- Magnesium, pyridoxine for 1 tablet 3 times a day during 1 month.

PROSPECTS FOR FUTURE STUDIES

In the daily practice of a cardiologist, it is rarely possible to meet patients younger than 30 with a persistent AF. In this clinical case, the features of the course and methods of diagnosis of AF with a concomitant myocardial bridge in a young patient after radiofrequency ablation are displayed.

REFERENCES

1. Sychev O.S. Fibrillyaciya predserdij. Sovremennye podhody k lecheniyu i profilaktike oslozhnenij u pacientov s soputstvuyushchej patologiej serdca. / Sychev O.S. // Ukraïns'kij medichnij chasopis / Sychev O.S. – Kiev, Ukraina: OOO «Morion», 2011. – (6). – S. 54–58.
2. . Belyalov F. I. Fibrillyaciya predserdij. / Belyalov F. I. // Aritmii serdca / Belyalov F. I. – Rossiya, Irkutsk: RIO IGMAPO, 1996. – (5). – S. 45–50.
3. Mandel V. Dzh. Glava 7. Predserdnye narusheniya ritma: osnovnye koncepcii / Mandel V. Dzh // Aritmii serdca. Mekhanizmy, diagnostika, lechenie. / Mandel V. Dzh. – Rossiya, Moskva: Medicina, 1996. – (t. 1). – S. 346–379.3. Mandel V.
4. Diagnostika i lechenie fibrillyacii predserdij / Syrkin A. L., Sulimov V. A., Fomina I.G. ta in.]. // Kardiovaskulyarnaya terapiya i profilaktika. – 2005. – № 4. – S. 347–356.
5. Miokardial'nye mostiki / Bokeriya L. A, Suhanov S. G., Sternik L. I, SHatahyan M. P. – Rossiya, g. Perm': NCSSKH im. A. N. Bakuleva RAMN, 2013. – S. 158.
6. Korotaev D. A. Miokardial'nye mostiki:sovremennoe sostoyanie problemy / Korotaev D. A. // Patologiya krovoobrashcheniya i kardiohirurgiya. – 2012. – № 1. – S. 85–89.
7. Belov YU.V., Bogopol'skaya O.M. Miokardial'nyj mostik — vrozhdennaya anomaliya koronarnogo rusla / Belov YU.V., Bogopol'skaya O.M. // Kardiologiya. – 2004. – № 12. – S. 89–94.

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THE IMPORTANCE OF THE INDIVIDUAL APPROACH TO THE PATIENT ON THE EXAMPLE OF CLINICAL CASE

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Any disease is the result of the interaction of pathologic process and the patient's personality, so the basis of optimal treatment strategy is physician and patient partnership in the fight for recovery and/or the most beneficial progress of chronic diseases with the highest possible quality and life expectancy. The implementation of this postulate is only possible with correct diagnosis, which presents some difficulties in this case. Due to individual approach we were able to find the optimal treatment and not to harm the patient. We recommend for all who works in practical medicine to put into the basis of the treatment, first of all, the patient's personality.

KEY WORDS: individual approach to the patient, formation of right atrium, optimal treatment

ВАЖЛИВІСТЬ ІНДИВІДУАЛЬНОГО ПІДХОДУ ДО ПАЦІЄНТА НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Будь-яка хвороба є результат взаємодії патологічного процесу і індивідуальності пацієнта, тому основу оптимальної тактики лікування становить партнерство пацієнта і лікаря в боротьбі за одужання і/або максимально сприятливий хронічний перебіг хвороби з максимально можливими якістю і тривалістю життя. Реалізація даного постулату можлива тільки при постановці правильного діагнозу, що представляло певні труднощі в нашому випадку. Завдяки індивідуальному підходу нам вдалося підібрати оптимальне лікування і не нашкодити пацієнту. Рекомендуємо всім працюючим в практичній медицині ставити в основу лікування, перш за все, індивідуальність пацієнта.

КЛЮЧОВІ СЛОВА: індивідуальний підхід до пацієнта, утворення правого передсердя, оптимальне лікування

ВАЖНОСТЬ ИНДИВИДУАЛЬНОГО ПОДХОДА К ПАЦИЕНТУ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Любая болезнь есть результат взаимодействия патологического процесса и индивидуальности пациента, поэтому основу оптимальной тактики лечения составляет партнерство пациента и врача в борьбе за выздоровление и/или максимально благоприятное хроническое течение болезни с максимально возможными качеством и продолжительностью жизни. Реализация данного постулата возможна только при постановке правильного диагноза, что представляло некоторые трудности в нашем случае. Благодаря индивидуальному подходу нам удалось подобрать оптимальное лечение и не навредить пациенту. Рекомендуем всем работающим в практической медицине ставить в основу лечения, прежде всего, индивидуальность пациента.

КЛЮЧЕВЫЕ СЛОВА: индивидуальный подход к пациенту, образование правого предсердия, оптимальное лечение

INTRODUCTION

A patient (Latin «patiens» – suffering, enduring) is a person who receives medical care and uses medical services regardless of the presence or absence of a disease [1].

The goal of any medical procedure is to achieve the best clinical result with the greatest possible improvement in the quality and life span of the patient while minimizing the cost of therapy [2]. The basis of the approach is the cooperation of the doctor and patient in all spheres of life of the latter. We vividly elaborated the importance of an individual approach to the patient on the example of this clinical case.

OUR PATIENT

Passport data: a man, 52 years old, a resident of the city, a pensioner.

At the time of admission, he complained of piercing pain in the middle third of the rib cage on the left that occurs when weather changes. Pain lasts for several hours, does not irradiate, disappears spontaneously or after taking isosorbide dinitrate, there is no connection between chest pain and physical exertion; rhythmic heartbeat, appears mainly with excessive physical exertion, lasting up to 10 minutes, disappearing spontaneously; rare episodes of single extrasystole without any clinical manifestations lasting up to several minutes; dyspnea when performing excessive physical exertion, disappears at rest within 3–5 minutes.

ANAMENESIS OF THE DISEASE

Till May 2014 there were no complaints from the cardiovascular system: blood pressure was not monitored properly, during medical examination at work, the indicators were recorded within the limits of normotension or hypotension; suffered acute Q-positive anterior myocardial infarction from 09.05.14; he was treated repeatedly as an outpatient and inpatient at the place of residence; last month, he took aspirin, atorvastatin, isosorbide dinitrate when the need arises. His current visit to the hospital was planned for the purpose of medical examination and if necessary, correction of therapy.

ANAMNESIS OF LIFE

In 2009 during esophagogastroduodenoscopy erosive gastritis was detected without accompanying clinical manifestations, there was no treatment prescribed, no medical documentation was provided; smoked for 20 years about 20 cigarettes a day, quitted smoking from 09.05.14. Diabetes mellitus, Botkin's disease, had no history of tuberculosis. There was no allergy.

OBJECTIVE STATUS

The general condition is satisfactory, the consciousness is clear, the patient is active. BMI = 21 kg/m^2. Skin and visible mucous membranes without features. Peripheral lymph nodes are not enlarged. The thyroid gland is not clearly defined. Musculoskeletal system without features. On percussion of lungs, a pulmonary sound, on auscultation breathing is vesicular. Sinus rhythm, muffled tones, pulse = heart rate = 65 beats/min, BP on both hands 120/80 mm Hg. The abdomen is of normal size, soft, painless. The liver is at the edge of the costal arch, painless. No abnormalities in physiological functions (according to the patient). Negative Pasternatsky's symptom on both sides. Absent shin Edema.

PLAN OF SURVEY

Clinical blood test, a clinical urine analysis, a biochemical blood test (total cholesterol, bilirubin, AlAT, AsAT, fasting blood serum glucose, creatinine, urea, potassium, sodium), chest X-ray, ECG, ultrasound of the heart, daily monitoring of ECG and blood pressure.

SURVEY RESULTS

Clinical blood test: the parameters are within the normal range.

Clinical analysis of urine: parameters are within the normal limits.

Biochemical blood test: hypercholesterolemia.

Chest X-ray: Absence of Focal and infiltrative changes in the lungs. The root structures are not expanded. Sinuses are clear. The diaphragm is clearly delineated. The heart is of normal shape and size. The aorta is not changed.

ECG: Sinus rhythm, regular, heart rate 54 beats/min (bradycardia). Scarring of the myocardium in the apical anterior-septal region. Q wave is positioned in the III standard lead. The disturbance of repolarization processes is diffuse.

Daily monitoring of ECG and blood pressure: During the whole period of observation against the background of a sinus rhythm the patient had an average heart rate of 67 beats/min, single supraventricular and ventricular extrasystoles were recorded. Ischemic ECG changes are not recorded. The systolic and diastolic blood pressure are characteristic for normotension throughout the observation period.

Echocardiogram (one month before admission, provided by the patient): Sclerotic changes in the walls of the aorta, valves of the aortic and mitral valves. Dilation of the left atrium. Dilation of the ascending aorta. Hypertrophy of myocardium of the left ventricle. Hypokinesia of the myocardium of the interventricular septum, apex and antero-lateral wall of the LV. Aneurysm of the upper left ventricle and apical segment of the interventricular septum. Pathological formation in the cavity of the right atrium (thrombus? myxoma?) with the size 26,6×8,8 mm. EF 38 %.

Echocardiography (in current hospitalization): Sclerotic changes in the walls of the aorta, valves of the aortic and mitral valves. Dilation of the left atrium. Dilation of the ascending aorta. Hypertrophy of myocardium of the left ventricle. Hypokinesia of the myocardium of the interventricular septum, apex and antero-lateral wall of the LV. Aneurysm of the upper left ventricle and apical segment of the interventricular septum. EF 43 %. No relevant information in cavity of the right atrium was obtained.

Echocardiography (again in the present hospitalization): Sclerotic changes in the walls of the aorta, valves of the aortic and mitral valves. Dilation of the left atrium. Dilation of the ascending aorta. Hypertrophy of myocardium of the left ventricle. Hypokinesia of the myocardium of the interventricular septum, apex and antero-lateral wall of the LV. Aneurysm of the upper left ventricle and apical segment of the Interventricular septum. Vascular network Chiari in the cavity of the right auricle. EF 41 %.

Exercise stress test: the presence of myxoma/right atrial thrombus is a relative contraindication to the conduct of this test, so the procedure was not performed.

CLINICAL DIAGNOSIS

CHD: Atherosclerosis of the aorta. Postinfarction (09.05.14 Q-positive antero-posterior-apical) cardiosclerosis. Aneurysm of the tip of the left ventricle. Aneurysm of the apex segment of the interventricular septum. Formation of the right atrium (?). HF stage I 1st functional class with reduced systolic function of the left ventricle.

RECOMMENDED TREATMENT

Modification of lifestyle: dieting, regular physical activity.

Drug therapy: clopidogrel 75 mg in the afternoon until May 2015, aspirin 75 mg in the evening, atorvastatin 20 mg at night, nebivolol 2.5 mg in the morning, ramipril 2.5 mg in the morning.

RECOMMENDED SURVEYS

Lipid profile and exercise stress test after final diagnosis

Any disease is the result of the interaction of the pathological process and the individuality of the patient [3], therefore the basis of the optimal treatment tactic is the partnership of the patient and the doctor in the struggle for recovery and / or the most favorable chronic course of the disease with the highest possible quality and life expectancy [2]. Implementation of this postulate is only possible with the formulation of the correct diagnosis, which presented some difficulties in our case in view of the ambiguous results of echocardiography.

In favor of expectant management regarding the formation of the right atrium, the absence of clinical signs of any of the presumed structures of the right auricle, a significant harm to the patient's health when choosing empirical treatment of the assumed formations.

OUR TACTICS OF TREATMENT: RESULTS

We regularly made telephone visits, negative dynamics of the patient’s health was not observed.

In January 2015, spiral computed tomography of the heart with contrast was performed, no formations of the right atrial cavity and Chiari vasculature were detected.

We hurried slowly and respected the basic law of medicine – do no harm. We recommend everyone to rely on an individual approach to the patient in real clinical practice.

REFERENCES

1. Oxford dictionaries [electronic source] // Access mode: http://www.oxforddictionaries.com/
2. Ashcroft R. The Goals of Medicine: The Forgotten Issue in Health Care Reform / R. Ashcroft // J Med Ethics. – 2000. – № 26. – p. 293–294.
3. Boorse C. Concepts of health and disease / C. Boorse // Philosophy of Medicine. – NY: Springer, 2011. – p. 13–64.

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CHRONIC RENAL DISEASE AS A CAUSE OF CARDIOVASCULAR PATHOLOGY

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The issues of etiology of development of cardiac changes in renal dysfunction, diagnostics and establishment of clinical diagnosis are reviewed as illustrated by a clinical case. Recommendations on lifestyle modification and medicament treatment tactics are described.

KEY WORDS: chronic pyelonephritis, coronary heart disease, arterial hypertension, cardiac failure

ХРОНІЧНА ХВОРОБА НИРОК ЯК ПРИЧИНА ВИНИКНЕННЯ СЕРЦЕВО-СУДИННОЇ ПАТОЛОГІЇ

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На прикладі клінічного випадку розглянуто питання етіології розвитку кардіальних змін при нирковій дисфункції, діагностику і встановлення клінічного діагнозу. Описано рекомендації з модифікації способу життя, а також тактику медикаментозного лікування.

КЛЮЧОВІ СЛОВА: хронічний пієлонефрит, ішемічна хвороба серця, артеріальна гіпертензія, серцева недостатність

ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК КАК ПРИЧИНА ВОЗНИКНОВЕНИЯ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

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На примере клинического случая рассмотрены вопросы этиологии развития кардиальных изменений при почечной дисфункции, диагностику и постановку клинического диагноза. Описано рекомендации по модификации образа жизни, а также тактику медикаментозного лечения.

КЛЮЧЕВЫЕ СЛОВА: хронический пиелонефрит, ишемическая болезнь сердца, артериальная гипертензия, сердечная недостаточность

INTRODUCTION

Multiple studies have proven that renal dysfunction [1] is an independent predictor of cardiovascular morbidity.

Even a mild renal pathology, irrespective of its etiology, considerably increases the risk of arterial hypertension, coronary heart disease (CHD), cardiac failure, and cardiovascular death [2].

The risk of cardiovascular complications occurs not only at renal failure terminal stage, but also at early stages of renal function decrease [3]. This is due to complex effect of hemodynamic, metabolic, and endocrine disorders associated with renal dysfunction on myocardium and vessels [4]. The interrelation between renal function and cardiovascular system condition is obvious, which allows not only combining kidney and heart affection and chronic cardiac failure development into cardiorenal continuum, but also introducing the concept of «cardiorenal syndrome» into clinical practice [5]. Its essence is as follows: kidney or heart dysfunction with acute or chronic development pattern aggravates the failure of

each organ, thus increasing mortality due to cardiac or renal pathology [6].

The renal pathology in the examined clinical case is chronic pyelonephritis. This is a slowly progressing, occasionally exacerbating bacterial inflammation of renal interstitial, which leads to irreversible changes in pelvicalyceal system, as well as to elevated blood pressure and chronic renal failure [7]. Chronic pyelonephritis can be either a consequence of incurred acute pyelonephritis or a primary chronic process [8].

Renal parenchyma infection occurs via hematogenous pathway from remote foci (in furunculosis, carbunculosis, abscess etc.) or via ascending urinogenous pathway (in cystitis, urethritis, prostatitis).

OBJECTIVE

The aim of the research is demonstration of particulars of managing a patient with complex cardiac pathology by an example of the represented clinical case.

OUR CASE

Case history of a man 54 years old.

Complaints. Thoracalgias of pressing nature (lasting about 3–5 minutes) appear at walk up to 200 m. They have predominantly retrosternal location. They are arrested by nitroglycerine after 2–3 minutes. Dyspnea appears both after walk and at rest. Headaches develop mainly at blood pressure elevation. They are arrested by citramonum after 20 minutes. Weakness. Palpitation attacks lasting for a few minutes to an hour, which develop upon blood pressure elevation. Cough with expectoration of a little sputum. Polyuria up to 2 l a day. The patient presents no complaints from other organs and systems.

Disease history. In 1999, the patient underwent surgery due to the left kidney carbuncle. Later, the patient was diagnosed with chronic pyelonephritis. The patient reports episodes of blood pressure increase since 2005; the maximum blood pressure was 220/140 mm Hg. He did not receive any treatment. Since June 2007, the patient has noticed the appearance of palpitations episodes associated with blood pressure elevation, which are accompanied with weakness, shortness of breath, and cough with expectoration of a little sputum. In August 2007, the patient received treatment in cardiologic department of the Central Clinical Hospital, where he was diagnosed with: persistent form of auricular flutter. Acute left ventricular insufficiency. Pulmonary edema. Cardiac failure degree 2A. The patient's condition was improved as of the moment of discharge, and sinus rhythm was restored as a result of urgent defibrillation. In 2010, the patient was hospitalized to the Central Clinical Hospital with complaints about pain in cardiac area, which he could not arrest on his own, and palpitations. He underwent a treadmill test with a positive result. Coronaro-ventriculography (CVG) was performed, and multivessels disease of coronary bed has been identified. Coronary artery bypass graft (CABG) surgery (3 bypasses) was performed. In July 2015, a new palpitation attack took place. The patient was urgently hospitalized to the Department of Intensive Care. The patient was diagnosed with cardiac rhythm disorders – persistent atrial fibrillation (AF) has been identified, for which catheter ablation was performed. The patient's condition has improved subsequent to the treatment performed. It was recommended to continue intake of anti-arrhythmic drugs (metoprolol 100 mg in the morning, losartan + hydro-chlorothiazide 50 mg twice daily, nifedipine 40 mg in the evening).

Life history. The patient's living conditions are satisfactory. He denies any pernicious habits. The patient's medication history and history of allergies are not aggravated. The patient denies a history of tuberculosis, viral hepatitis A, diabetes mellitus, psychic and venereal diseases. His heredity is aggravated in terms of cardiovascular diseases – coronary heart disease and arterial hypertension.

Objective status. The patient's condition is of moderate severity, his consciousness is clear, and his position is active. The patient's constitutional type is normosthenic. His height is 185 cm, his body weight is 78 kg, and the body mass index is 22.9. His cutaneous coverings are typical, pale pink. The lymph nodes available for palpation are not enlarged. The thyroid gland is not clearly identifiable. Palpation is painless. The locomotor system is unremarkable. Pastosity of lower extremities is at the ankle level.

Respiratory system. The chest is normosthenic. Condition after sternotomy. Percussion: dullness of lung sound in posterior lower lung portions along the scapular line at the level of rib IX on the left and along the paraspinal line at the level of rib X. Auscultation: rales in lower lung portions

associated with decreased vesicular respiration. Respiratory frequency – 23 per minute.

Cardiovascular system. The apex beat is located in intercostal space V along the left midclavicular line, diffuse (up to 3 cm). At topographic percussion, the left border of relative heart dullness is located in intercostal space v along the midclavicular line, and the right one and the upper one are unaltered. The cardiac activity is rhythmic. The heart sounds are muffled. Heart rate = pulse – 110/min. Blood pressure 180/120 mm Hg.

The abdomen has typical dimensions, it is soft and painless. The liver is located at the costal arch margin, it is painless. Costovertebral angle tenderness is negative on the both sides.

RESULTS OF THE SURVEY

Clinical blood count (20.02.17): Hb – 162 g/l; erythrocytes – $5.12*10^{12}$/l; leukocytes – $12.2*10^{9}$/l; ESR – 7 mm/h; eosinophils – 2 %; neutrophils: stab – 11 %, segmented – 78 %; lymphocytes – 7 %; monocytes – 4 %; platelets – 344 g/l; hematocrit – 48 %.

Urinalysis (20.02.17): Relative density – 1.007; protein – not identified; glucose – not identified; leukocytes 5–7 in the field of vision; pH – 6.0.

Blood chemistry panel (20.02.17): Total bilirubin – 16.5 μmol/l; AST – 22 U/l; ALT – 13 U/l; creatinine – 111.98 μmol/l; urea – 7.7 mmol/l; glucose – 7.5 mmol/l. Glomerular filtration rate measured by Cockcroft-Gault method – 75.5 ml/min.

Chest X-ray examination results (23.02.17): No focal or infiltrative changes are identified in lungs. Pleuropericardial cords are seen on the left. Venous hyperplasia signs are identified. The roots are structured and not enlarged. The sinuses are patent. The diaphragm is clearly delineated. The heart is expanded on the left. The aorta is unremarkable. Condition after sternotomia.

ECG results (22.02.17): The rhythm is sinus, regular. The heart rate is 73 bpm. Complete left bundle-branch block.

EchoKG results (23.02.17): Sclerotic changes of aorta walls, aortic and mitral valve cusps. Left ventricular myocardial hypertrophy. Dilation of cavities of both atriums. Regurgitation on pulmonary artery valve, degree I-II. Ejection fraction – 65 %.

Daily ECG and BP monitoring results (26.02.17): ECG: predominant rhythm is sinus, with average heart rate 73 bpm at daytime and 71 bpm at night. The circadian index is 1.02 %. Rigid circadian heart rate profile, vegetative denervation signs. Individual ventricular extrasystoles (1072) were registered during observation period. No ischemic changes are identified via ECG. Blood pressure: average daily BP is 133/83 mm Hg (min 105/56 mm Hg, max 160/90 mm Hg). Circadian index of systolic BP is 14 %. Circadian index of diastolic BP is 17 %. The patient belongs to the group with normal nocturnal blood pressure decrease.

Ultrasonic examination of kidneys (24.02.17): Contracted left kidney. Cyst of the left kidney. Microcalculosis of kidneys.

CLINICAL DIAGNOSIS

Coronary heart disease: stable effort angina of functional class III. Atherosclerosis of coronary arteries (coronaroventriculography dated 09.12.10). Coronary artery bypass graft – 3 bypasses (26.12.10). Renal arterial hypertension of III stage, 3 degree. Hypertensive heart. Persistent form of atrial fibrillation. Catheter ablation (2015). Cardiac failure stage II A, functional class II. Chronic renal disease of stage II. Carbuncle of the left kidney (1999). Urolithiasis. Secondary pyelonephritis, remission stage. Secondary contracted kidney. Cyst of the left kidney.

TREATMENT PLAN

1) Lifestyle modification:

– Change of daily routine (sleep duration not less than 8 hours a day).

– Dieting and following of recommendations on tolerable physical activity for this angina pectoris functional class. The main training technique in this case is slow walking without acceleration, at the rate below the pain threshold; after improvement of the patient's condition, achievement of walking rate 3–3.5 km/h can be deemed quite satisfactory. Duration of such exercise may comprise 20 to 60 min depending on the patient's condition severity. At home setting, the patient is recommended to perform respiratory and mild physical exercise 1–2 times daily.

2) Medicament therapy: Aspirin 75 mg; Valsartan 80 mg in the morning and 80 mg in the evening under blood pressure monitoring on a long-term basis; Hydrochlorothiazide 12,5 mg in the morning under blood pressure monitoring on a long-term basis; Atorvastatin 20 mg in the

evening; Amlodipine 5 mg twice daily under blood under blood pressure monitoring.

CONCLUSIONS

This clinical case reflects the peculiarities of incessant progression of combined cardio-vascular pathology developed in association with chronic renal disease, as well as diagnostics and treatment methods.

REFERENCES

1. Herzog C. Kidney disease in cardiology / C. Herzog // Nephrology Dialysis Transplantation. – 2010. – № 25. – P. 356–360.
2. Mukhin N.A. Nephrogenic arterial hypertension / N. A. Mukhin, N. A. Kozlovskaia // Doctor. – 2004. – № 10. – P. 4–7.
3. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis / [K. Damman, M. Valente, A. Voors, et al]. // European Heart Journal. – 2014. – № 35. – P. 455–469.
4. Incident atrial brillation and risk of end-stage renal disease in adults with chronic kidney disease / [N. Bansal, D. Fan, C. Y. Hsu, et al]. – 2013. – № 127. – P. 569.
5. Bagshaw S. Renal replacement therapy: when to start / S. Bagshaw, R. Wald // Contrib Nephrol. – 2011. – № 174. – P. 232–241.
6. Korotkyi D.V. Arterial hypertension and myocardial hypertrophy at pre-dialysis stage of chronic renal disease and in replacement renal therapy / D.V. Korotkyi, T. I. Makeeva, O. P. Zavaritskaia // Nephrology and Dialysis. – 2009. – № 11. – P. 251–257.
7. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization / [A. Go, G. Chertow, D. Fan, et al]. // ACC Current Journal Review. – 2004. – № 13. – P. 13.
8. Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention / [R. T. Gansevoort, R. Correa-Rotter, B. R. Hemmelgarn, et al]. // The Lancet. – 2013. – № 382. – P. 339–352.

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THE FIRST CASE OF ATRIAL FIBRILLATION: APPROACH ISSUES

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On the example of the clinical case of newly diagnosed atrial fibrillation, against the background of ischemic heart disease, diagnostic issues, clinical diagnosis, treatment tactics were considered. The emphasis was placed on the importance of lifestyle, the need for outpatient monitoring, timely examination and correction of patient treatment, including surgical intervention.

KEY WORDS: ischemic heart disease, atrial fibrillation

ПЕРШИЙ ЕПІЗОД ФІБРИЛЯЦІЇ ПЕРЕДСЕРДЬ: ПИТАННЯ ТАКТИКИ

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На прикладі клінічного випадку вперше виявленої фібриляції передсердь, на тлі ішемічної хвороби серця розглянуті питання діагностики, встановлення клінічного діагнозу, тактики лікування. Поставлені акценти на значенні способу життя, необхідності амбулаторного спостереження, своєчасному обстеженні та корекції лікування пацієнта, в тому числі і хірургічного.

КЛЮЧОВІ СЛОВА: ішемічна хвороба серця, фібриляція передсердь

ПЕРВЫЙ ЭПИЗОД ФИБРИЛЯЦИИ ПРЕДСЕРДИЙ: ВОПРОСЫ ТАКТИКИ

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На примере клинического случая впервые выявленной фибрилляции предсердий, на фоне ишемической болезни сердца рассмотрены вопросы диагностики, установления клинического диагноза, тактики лечения. Поставлены акценты на значении образа жизни, необходимости амбулаторного наблюдения, своевременном обследовании и коррекции лечения пациента, в том числе и хирургического.

КЛЮЧЕВЫЕ СЛОВА: ишемическая болезнь сердца, фибрилляция предсердий

INTRODUCTION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by chaotic atrial electrical activity, high heart rate (> 350 bpm) and irregular ventricular rhythm (with no total AV blockade), with ineffective atrial contractions which is associated with an increased risk of thromboembolism. AF is the most common persistent cardiac arrhythmia, frequency of which in the general population is 1–2 % [1–2].

AF affects more than 6 million people in Europe and its prevalence in the next 50 years will at least double, considering aging of the population.

AF increases the risk of stroke by 5 times, and every fifth stroke develops against the background of this arrhythmia. In patients with AF ischemic stroke often end with death, leads to more severe disability and recurs more often than in patients with a stroke of a different nature. Accordingly, the risk of death in patients with stroke associated with AF increases by 2 times and the financial costs of treatment – by 1.5 times.

Prevalence of AF increases with age: from < 0.5 % at the age of 40–50 years to 5–15 % at the age of 80 years [3–7]. This arrhythmia

develops more often in men than in women. The risk of developing AF is about 25 % after 40 years [8]. Prevalence and incidence of AF among representatives of the non-European race have been studied worse.

In most patients, AF progresses steadily with the development of persistent or permanent forms against the background of the development of the underlying disease. Earlier diagnosis of arrhythmia would allow prescribing medications timely to prevent not only the effects of arrhythmia, but also the progression of AF with the development of refractory arrhythmia [1, 9–10].

The main risk factors for AF are age over 65 years, arterial hypertension (AH), coronary heart disease (CHD), structural heart disease (valvular dysfunction, hypertrophic cardiomyopathy, systolic/diastolic heart dysfunction, chronic heart failure (CHF), hyperthyroidism, obesity, diabetes, chronic obstructive pulmonary disease (COPD), sleep apnea, chronic kidney disease.

In the tactics of the introduction of patients, key points are singled out: emergency reduction of the first occurrence of an attack (ensuring optimal blood pressure (BP) and sinus rhythm)); eliminating provoking factors (lifestyle modification, treatment of previous cardiovascular diseases); strokes risk assessment (prescription of oral anticoagulants to high-risk patients); blood pressure evaluation and the prescription of appropriate therapy; eliminating the main symptoms (antiarrhythmic drugs, cardioversion, catheter ablation) [1, 10].

CLINICAL CASE

The patient is 59 years old, occupies an administrative job, complains of exertional dyspnea while climbing the stairs to the 4th floor, unproductive paroxysmal cough after considerable physical exertion (skiing), shins swelling in the evening, increased fatigue, a feeling of general weakness.

Antecedent anamnesis: 03.2006 – for the first time a constricting sternal pain, short breath when climbing to the 7th floor with a stop at the 3rd. Symptoms were relieved after 1 tablet of nitroglycerin (0.5 mg). 18.03.2006 - the heart pain becomes more intense. There's no relief after nitroglycerin. The ambulance delivered the patient to the cardiological department of the hospital with an urgent diagnose of «acute myocardial infarction». The hospital diagnosis: «IHD: acute (18.03.06) Q-positive transmural myocardial posterior infarction. Subocclusion of the right coronary artery. 30 % stenosis of the right interventricular brunch. Hypertensive disease, stage III». 11.05.06. – RCA stenting. The patient controlled BP irregularly, led an active lifestyle, was fond of mountain skiing and worked in an administrative position. 5.01.2017. – abrupt short breath when climbing the stairs to the 5th floor, relieved after a short rest. The symptom occurred repeatedly within the next two weeks. 23.01.2017. – Atrial fibrillation was registered for the first time on the ECG in a clinic. 26.01.2017. – hospitalization in the cardiological department of the hospital for examination and selection of adequate therapy.

Patient anamnesis: Profession: radio engineer. At the age of 17 the patient underwent tonsillectomy. The patient smoked at the age of 45–50 years (1 pack/month for 5 years). Tuberculosis, diabetes mellitus, venereal diseases, rheumatism, oncological, psychiatric illnesses, severe traumas are disclaimed by the patient.

At the age of 16–17 – Botkin's disease.

Burdened hereditary anamnesis: father - stable angina, hypertension. He died to a stroke at the age of 79 years. Mother – cancer of the gallbladder. The allergic anamnesis is not burdened.

Objective status: The general condition is relatively satisfactory. Consciousness is clear. The position is active. Emotionally stable. Hypersthenic. Height 176 cm, body weight 100 kg. BMI = 32.3 (obesity of the I degree). Skin covers, visible mucous are pure, pale pink. Peripheral lymph nodes are not palpable. Thyroid gland is moderately enlarged, painless on palpation. CVS: heart rate is 80, pulse 61 beats/min, pulse deficit is 19. BP on the left arm is 135/80 mm Hg. BP on the right arm is 140/80 mm Hg against the background of antihypertensive therapy. During percussion the boundaries of relative cardiac dullness are uniformly widened: the left border is in the 6th intercostal space, 1 cm outward from the midclavicular line, the right border is in the 4th intercostal space, 2.5 cm righter from the sternum, the upper border is in the 2nd intercostal space. At auscultation heart sounds are muffled, arrhythmic, there is an accent of the second tone over the aorta. Respiratory system: BR – 16. Percutally above the lungs a clear pulmonary sound is identified.

Auscultatory: vesicular breathing above the entire surface of the lungs. The tong is clear and moist. The abdomen is soft, enlarged in volume due to subcutaneous fat, painless during palpation. The liver protrudes 1 cm from under the edge of the costal arch, painless during palpation. The symptom of effleurage in the lumbar region is negative on both sides. Moderate edema of both lower limbs in the region is determined.

Laboratory findings: Clinical blood analysis (from 02.02.2017): increase in hemoglobin (Hb – 169 g/l), insignificant erythrocytosis (5,91 g/l), lymphocytosis (l–38,6 %), increase in hematocrit (Ht – 51,0). Clinical urine analysis (from 01.21.2017): the indices within the limits of the norm, except for insignificant proteinuria – 0, 043 g/l. Biochemical blood test (from 01.21.2017): the parameters are within the norm except for the increase in the level of urea (90 mmol/l), aminotransferases (ALT-6 U|L, AST-43 U|L), hyperkalemia (K – 5.19 mmol/L), increased atherogenicity coefficient (4,1) and lowered HDL cholesterol level (0,78 mmol/l). Thyroid hormones analysis (from 30.01.2017) – all indicators are within the norm.

Instrumental diagnostics: ECG (from 01/26/2017): atrial fibrillation, heart rate 73 b/min. Cicatricial changes in the myocardium of the left ventricle in the region of the posterior wall. Nonspecific intraventricular conduction abnormalities. Echocardiography. The dynamics of the results is presented in Table 1.

Table 1

Dynamics of EchoCG results

Factor	2006	2017
Myocardial hypertrophy	in the left ventricle only	in both of the ventricles
Dilatation of cordial cavities	not revealed	dilatation of all cavities
Atherosclerotic Changes	in the aorta only	in the aorta, aortic and mitral valve
Dyskinesia	akinesia of the posterior-apex-lateral segment of myocardium	akinesia in the posterior, posterolateral and basal walls of the left ventricle
Pathological regurgitation	not revealed	mitral regurgitation of II-III degree; tricuspid regurgitation of the I degree
Ejection fraction	61 %	44 %

Ultrasound of internal organs (from 01/30/2017): Diffusive changes in the liver and pancreas. Diffusive changes in the liver parenchyma with its enlargement by the type of fatty hepatosis. Polyp, kink and stagnation gallbladder. Microrolithiasis. Hyperplasia of thyroid gland, degree II. Cysts of both parts of the thyroid gland. Parathyroid hyperplasia on the right.

Daily monitoring of ECG (from 30.01.17): during all monitoring, atrial fibrillation was recorded with an average heart rate of 71 b/min with single and paired ventricular extrasystoles. Supraventricular ectopic activity, «the mixed type». Ventricular ectopic activity is the «nocturnal type of arrhythmia». Circadian index – 1.09 (rigid rhythm).

Veloergometry (from 30.01.17): The maximum power of the proposed load is 50 W. The test is positive. The signs of coronary insufficiency in the form of ST elevation in lead III and aVF by 1.5 mm were revealed. Angina pain was not detected during the procedure.

Transesophageal echocardiogram (from 03.03.17): a thrombus in the left atrial appendage, no thrombi in the right ear and atrium were detected. In the front part of the NA a functioning oval aperture 0.15 cm in diameter was detected.

Consultation of an arrhythmologists KNIUS (from 03.03.17): The patient is recommended to restore the heart rate a month after anticoagulant therapy and repeated esophagus EchoCG.

Clinical diagnosis:

Basic diagnosis: IHD: postinfarction (18.03.2006 Q-positive posterior) cardio-sclerosis. PCA subocclusion. 30 % stenosis of the right interventicular brunch. PCA stenting (11.05.06). Hypertensive disease, stage III, the 2nd degree. Newly identified secondary atrial fibrillation. EHRA II, CHADS-VASc-2, HAS-

BLEED-1, CH I-IIA with diastolic LV myocardium dysfunction (EF 45 %). Very high additional cardiovascular risk.

Concomitant diagnosis: thyroid gland hyperplasia, the 2nd degree. Cysts of both parts of the thyroid gland. Parathyroid hyperplasia on the right. Diffusive changes in the liver with its enlargement by the type of fatty hepatosis, polyp of the gallbladder.

Recommendations for the patient approach: lifestyle modification; anticoagulant therapy; sinus rhythm control: cardioversion or heart rate control; treatment of arterial hypertension; treatment of heart failure; re-consultation of the arrhythmologists to determine the tactics of restoring rhythm.

Taking into account the thrombus in the left atrial appendage the patient should be treated with a vitamin K antagonist (INR 2.0–3.0) and repeat transesophageal echocardiography. If the thrombus is dissolved, cardioversion can be performed, after which lifelong therapy with oral anticoagulants is prescribed. If the thrombus persists, restoring the rhythm can be refused in favor of controlling the frequency of the ventricular rhythm, especially if the symptoms of AF are controlled, given the high risk of thromboembolism in the background of cardioversion [1].

Treatment plan:

Non-drug treatment: diet: restriction of the calorie value food, carbohydrates and fats, table salt, adequate volume of consumed liquid; physical activity (controlled physical activity); non-smoking, non-alcohol habits; body weight control.

Medication: Rivaroxaban 20 mg 1p/d; Nebivolol 2.5–5 mg/d in the morning under the control of the pulse and blood pressure (with SBP < 105 or pulse < 50 the drug should be canceled, ECG should be recorded and therapy correction is performed); Amlodipine 5 mg; Essentiale 1 caps. 2 p/d; resuming amiodarone 3 weeks later: if the pulse is 70 or more at 200 mg 2 times a day, if the pulse is less than 70 – 100 mg 2 times a day; re-conducting the ECHO-KG 4 weeks later. In the absence of thrombi in the atria, attempt to restore the rhythm (cardioversion) [1, 11].

CONCLUSIONS

The example of a clinical case shows the effect of excessive physical exertion and psychoemotional factors on the onset of atrial fibrillation and the progression of heart failure in a patient who underwent myocardial infarction. For the first time the emergence of atrial fibrillation, 11 years after the infarction, is not amenable to drug therapy. The further tactics of the patient's management will depend on the results of anticoagulant therapy and repeated esophageal echocardiography. Moreover, the strategy of monitoring the frequency of ventricular rhythm is not inferior to the rhythm control strategy for the effectiveness of prevention of cardiovascular mortality and morbidity [1, 12].

REFERENCES

1. Rekomendacii po fibrillatii predserdiy // ESC Guidelines for the management of atrial fibrillation, 2016.
2. Yabluchansky N. I. Oriented to a practical doctor classification of atrial fibrillation / N. I. Yabluchansky, L. A. Martimyanova // The Journal of V. N. Karazin Kharkiv National University, series «Medicine». – 2002. – Issue 4, № 546. – p. 6–11.
3. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew Paisley study / S. tewart, C. L. Hart, D. J. Hole, J. J. McMurray // Heart. – 2001. – Vol. 86, № 5. – P. 16–521.
4. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study // [A. S. Go, E. M. Hylek, K. A. Phillips, et al.] // JAMA. – 2001. – Vol. 285. – P. 2370–2375.
5. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence / [Y. Miyasaka, M. E. Barnes, B. J. Gersh, et al.] // Circulation. – 2006. – Vol. 114. – P. 119–125.
6. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study / [J. Heeringa, D. A. van der Kuip, A. Hofman, et al.] // Eur. Heart J. – 2006. – Vol. 27. – P. 949–953.
7. Increasing prevalence of atrial fibrillation and flutter in the United States / G. V. Naccarelli, H. Varker, J. Lin, K. L. Schulman // Am. J. Cardiol. – 2009. – Vol.104. – P. 1534–1539.
8. Lloyd-Jones D. M. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study / D. M. Lloyd-Jones, T. J. Wang, E. P. Leip // Circulation. – 2004. – Vol. 110. – P. 1042–1046.

9. Outcome parameters for trials in atrial fibrillation: executive summary. Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA) / [F. P. Kirchho, A. Auricchio, J. Bax, et al.] // Eur. Heart J. –2007. – Vol. 28. – P. 2803–2817.
10. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project / [G. Y. Lip, D. J. Golding, M. Nazir, et al.] // Br. J. Gen. Pract. – 1997. – Vol. 47. – P. 285–289.
11. Ricard Ph. Cardioversion of atrial fibrillation: How and when? / [Ph. Ricard, K. Yaïci, J.P. Rinaldi, et al.] // Eur. Heart. J. – 2003. – Vol. 5, Suppl. H. – P. H40–H44.
12. Van Gelder I. C. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation / I. C. Van Gelder, V. E. Hagens, H. A. Bosker // N. Engl. J. Med. – 2002. – Vol. 347. – P. 1834–1840.

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MASSIVE PULMONARY EMBOLISM IN OLDER PATIENT: SURVIVAL DESPITE STATISTIC DATA

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Massive pulmonary thromboembolism is presented in this article on example of clinical case. Clinical investigation, prognosis evaluation tools, diagnosis and acute phase treatment along with prevention of recurrent episode of pulmonary embolism presented. Observed and described clinical case of pulmonary embolism in older patient, when patient was mistakenly diagnosed in emergency department as acute coronary syndrome patient.

KEY WORDS: pulmonary thromboembolism, massive, older age, treatment, disease prevention

КЛІНІЧНИЙ ВИПАДОК МАСОВАНОЇ ТЕЛА У ПАЦІЄНТА ПОХИЛОГО ВІКУ: ВИЖИТИ ВСУПЕРЕЧ СТАТИСТИЦІ

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Масивна тромбоемболія легеневої артерії представлена в цій статті на прикладі клінічного випадку. Представлені методи встановлення діагнозу, інструменти для оцінки прогнозу, діагностика та лікування гострої фази поряд з профілактикою рецидивуючих епізодів захворювання. У статті представлений клінічний випадок легеневої емболії у пацієнта похилого віку, коли у відділенні невідкладної допомоги пацієнту був помилково поставлений діагноз гострий коронарний синдром хворого.

КЛЮЧОВІ СЛОВА: тромбоемболізм легеневої артерії, масивний, похилий вік, лікування, профілактика захворювання

КЛИНИЧЕСКИЙ СЛУЧАЙ МАССИВНОЙ ТЭЛА У ПОЖИЛОГО ПАЦИЕНТА: ВЫЖИТЬ ВОПРЕКИ СТАТИСТИКЕ

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Массивная легочная тромбоэмболия представлена в этой статье на примере клинического случая. Описаны постановка диагноза, инструменты оценки прогноза заболевания, диагностика и лечение острой фазы, а также методы профилактики повторного эпизода заболевания. Описан клинический случай тромбоэмболии легочной артерии у пациента пожилого возраста, когда в отделении неотложной помощи был ошибочно диагностирован острый коронарный синдром.

КЛЮЧЕВЫЕ СЛОВА: тромбоэмболизм легочной артерии, массивный, пожилой возраст, лечение, профилактика заболевания

INTRODUCTION

Pulmonary thromboembolism (PE) is an acute blockage of the trunk or branches of the arterial system of the lungs with a formed in the veins of the circulatory system or in the right side of the heart thrombus [1]. In 95 % of cases, PE is a consequence of deep vein thrombosis (DVT), therefore, in modern literature the term «pulmonary embolism» is often replaced by the term «venous thromboembolism» [1–2]. PE is the third most common type of pathology of the

cardiovascular system after ischemic heart disease and stroke. Long-term complication of PE reported in medical literature is chronic thromboembolic pulmonary hypertension with incidence of 0.1–9.1 % within the first two years after a symptomatic PE event [2].

CLINICAL CASE

A 73-year old man was admitted by ambulance in the emergency department (ED) of 25 Kharkiv city clinical multidisciplinary hospital with complains on sudden severe dyspnea in the slightest physical exertion, periodical burning pain in the heart area without clear connection with physical exertion ~ 15 min duration.

ANAMNESIS MORBI

All complains started a day ago, in anamnesis morbi remarkable were myocardial infarction in 2009, transition ischemic attack in January 2016, CAD history and arterial hypertension for many years (bisoprolol and aspirin were taken from time to time).

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, do not abuse alcohol.

OBJECTIVE EXAMINATION

Conciseness – clear, state – severe, body position – active. Patient was orientated in place, time, his personality. Pale skin and mucosae, cyanosis. Thyroid: no pathological changes. Musculoskeletal system – no pathological changes. Breath rate (BR) – 22–24 /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, others – within normal parameters. Heart auscultation: rhythmic, heart tones – muffled. Pulse – rhythmic, 120 bts/min. Blood pressure (BP) 110/90 mm Hg. Abdomen: normal size, symmetric, unpainful. Liver: liver margin is 5 cm below right rib cage, solid, no pain during palpation in right hypochondria. Spleen: normal. Pasternatsky symptom – negative from both sides. Edemas: right leg was edematous below knee joint comparing with left low extremities, leg slightly painful in edematous area during palpation.

In ED, preliminary diagnosis of unstable angina with community-acquired pneumonia was done because of significant leukocytosis ($19,5*10^9$/l) with left-side shift presented in complete blood count (CBC), symptoms and anamnesis morbi data of the patient, who hasn't took medication as it was needed. BR was 20–22 in min, heart rate (HR) around 120 bts in min, BP 110/90, low extremities – not very remarkable changes in left calf area. But clinical probability of pulmonary embolism according to American Academy of Family Physicians (AAFP) (score 13) [3] and the American College of Physicians (ACP) Scores (more than 6) [4] defined possibility of PE in this patient case as high probability (likely). It was possible because of: patient HR was > 95 in min, presence of unilateral lower limb pain with unilateral edema of left low extremity and patient's age was bigger than 65.

LABORATORY AND INSTRUMENTAL TESTS

CBC from 02-sep-2016: leukocytosis (white blood cells (WBC) – $19,5*10^9$/l) with left-side shift (bands – 6 %, segments – 76 %) and elevation of Erythrocytes sedimentation rate (ESR) – 37 mm/h.

CBC from 03-sep-2016: leukocytosis (white blood cells (WBC) – $13,8*10^9$/l) with left-side shift (bands – some, segments – 85 %) and ESR – 15 mm/h.

CBC from 07-sep-2016: no clinically significant changes except ESR level – 23 mm/h.

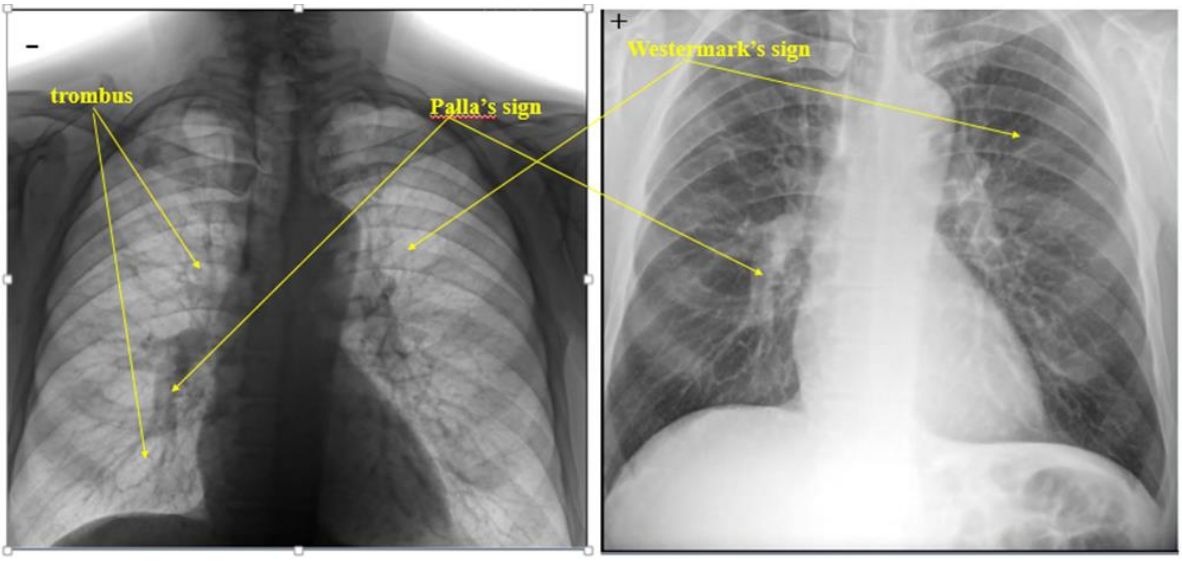
Urinalysis: no clinically significant changes except proteinuria – 0.216 g/l were found.

In biochemistry data significant were: hyperglycemia (fasting glucose levels 8,9 – 8,2 mmol/l), decreased prothrombin time levels (83 – 73,2 %) on the background of medication prescribed (enoxaparin natrium), normal level of Troponin I.

ECG showed classical ECG changes in PE patients as pathological S wave in lead I, Q wave with T-wave inversion in lead III (McGinn-White sign), QR pattern in V1 lead and new right bundle branch block, heart rate – 100 bts/min.

Despite that chest radiograph cannot exclude or confirm diagnosis of PE, but this investigation is useful in further investigations guideless and exclusion or definition of alternative diagnoses. In our patient Chest X-ray data was seen specific for PE Palla's sign

(enlarged right descending pulmonary artery. Diaphragm's cupulas are flattened [5]). Sinuses are poorly differentiated. Westermark sign was seen too (a focus of oligemia (leading to collapse of vessel [5]) seen distal to a pulmonary embolism). Conclusion was: 2-sided pulmonary thromboembolism. But X-ray specialist didn't recognized from the first examination these signs so diagnosis of PE in this patient case wasn't established immediately in emergency department (see pic.1).



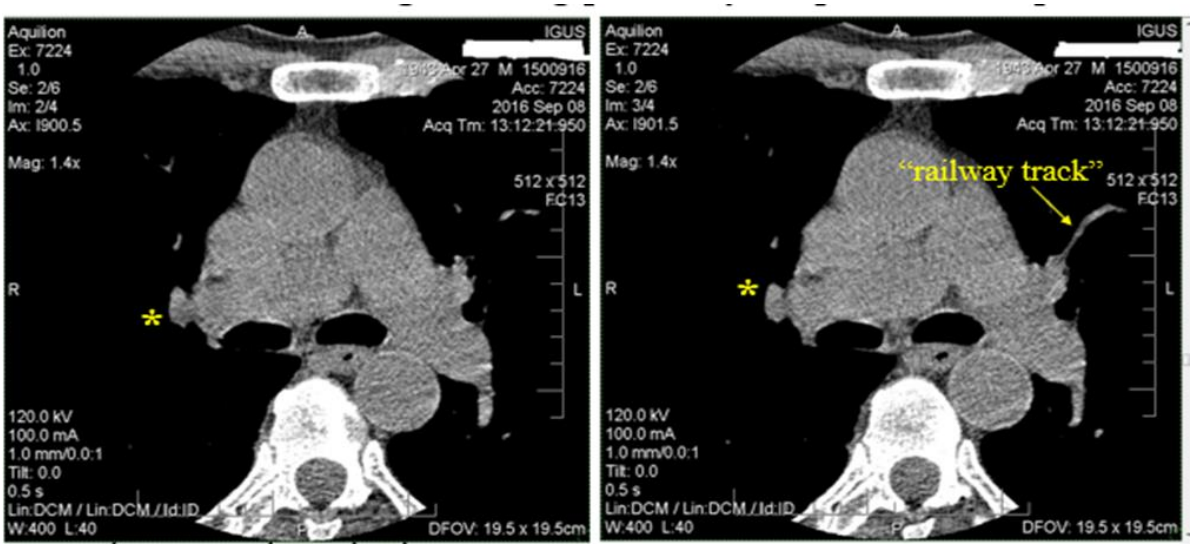
Pic.1 Chest X-ray data

Echocardiography of this patient: EF (ejection fraction) – 60 %. Normal wall movement, myocardium structure with pointed cardiosclerosis changes. Contractility function – not changed. Left Ventricle: FDD – 48 mm (N – 25–35 mm) – enlarged, FSD – 39 mm (N – 23–38 mm), posterior wall thickness – 13 mm (N – 6–13mm). Intraventricular septum size – 13 mm (6–11 mm) – enlarged. Right Ventricle: diameter – 36 mm (N – 9–20 mm) – enlarged, wall thickness – 5,0 mm (N – 2–4 mm) – enlarged, left atrium – not enlarged – 36 mm in diameter (N – till 38 mm), right atrium – enlarged – 50 mm in diameter, interatrial septum – not changed. Valvular apparatus is not changed, except tricuspid valve – regurgitation I degree. In the cavity of the right ventricle clearly seen hyperechogenic formations – clots. Conclusion: Diffuse cardiosclerosis. Aortic atherosclerosis. Hypertrophy of the left ventricle I degree. Dilation of the right heart chambers. Tricuspid regurgitation 1-st degree. Clots in the cavity of the right ventricle. Ultrasound signs of cystitis, chronic prostatitis.

According to the American College of Radiology 2011 guidelines, only multisite CT pulmonary angiography was considered as the gold standard for the detection of PE. [6–7]. For patient with high clinical probability of likely PE, as was seen in our clinical case, multi-detector CT angiography has become an established imaging technique according to the ECS guidelines of acute pulmonary embolism diagnosis and management [1] and the best investigation recommended to prove diagnosis of PE, comparing with not required D-dimer investigation. Guidelines suggest for patients at high risk to skip the D-dimer test and immediately refer patient to CT pulmonary angiography, because even negative D-dimer test result couldn't allow making diagnosis without imaging technics [8]. So plasma D-dimer tests are more useful and effective for patients with intermediate risk of a PE, but also may be not necessary for patients at low and high risk [8].

CT pulmonary angiography findings were: in the main branches of the pulmonary artery clearly seen defects of contrasting thicknesses up to 15 mm on the right and 11 mm on the left, which is spread on all lobular and segmental branches of the pulmonary artery with subtotal or partial occlusion of the lumen (a partial filling defect surrounded by contrast material, producing the «railway track» sign on longitudinal images of the vessel). In both lungs

are visualized subpleural areas of lung parenchyma lightening by the type of «frosted glass». The diameter of the pulmonary artery on both sides is increased (26 mm – pulmonary truncus, 27mm –right pulmonary artery). In the right atrium are visualized defects of contrasting with dimensions of 35×22 mm (thrombus). Conclusion: CT picture of bilateral massive pulmonary embolism (see pic.2)



Pic.2 CT pulmonary angiography

Since the majority of cases PE originates from deep vein thrombosis (VTE), for evaluation of this patient diagnosis and finding of the source of suspected thromboembolism could be useful to refer patient on compression ultrasound of the lower extremities deep veins because patient during objective examination had not very prominent signs and symptoms of deep veins thrombosis as edematous right leg below knee joint and pain in edematous area during palpation.

FINAL DIAGNOSIS

Acute massive pulmonary 2-sided embolism, stable. CAD: stable angina III functional class, post infarction (2009) and diffuse cardiosclerosis. Arterial hypertension III stage, 1st degree, very high risk. CHF 2 A stage with preserved function of LV (EF 59 %), IV D functional class by NYHA. Varicose vein disease of low extremities, right leg phlebitis.

TREATMENT RECEIVED IN HOSPITAL

Zofenopril 7,5 mg 1 time\day at night, nebivolol 2,5 mg 1 time\day morning, warfarin 2,5 mg 1 time\day from 13.09, ceftriaxone 1,0 g 2 times\day IM from 02.09 till 07.09 (preliminary diagnosis was Community-acquired pneumonia), clexan (enoxaparin natrium) 0,4ml (40mg) 2 times a day subcutaneous from 02.09 (preliminary diagnosis in ED was Unstable angina), ivabradin 7,5 mg 2 times\day from 02.09, atorvastatin 40 ml 1 time\day at night from 02.09.16.

RECOMMENDATIONS

According to the American College of Physicians newest guidelines for the evaluation of patients with suspected acute PE (2015), the following recommendations may be applicable for our patient after hospital discharge treatment and prevention of further episodes of PE [8]:

1. Clinical improvement of the patient with PE depends on several main key factors as: at least 3 months duration of anticoagulant treatment received after discharge from hospital, in case of withdrawal of anticoagulant treatment, if anticoagulants are stopped after 6 or 12 months, the risk of recurrence can be expected to be similar to that after 3 months and indefinite treatment reduces the risk for recurrent venous thromboembolism by about 90 % [9–10].
2. In identifying of patients with higher long-term relative risk of PE recurrence useful will be to pay attention at the main risk factors as one or more previous episodes of VTE,

presence of antiphospholipid antibody syndrome or hereditary thrombophilia or residual thrombosis in the proximal veins. Also as additional risk factor was reported the persistence of right ventricular dysfunction at hospital discharge confirmed by echocardiography [1, 8]

In 2016, in the updated American College of Chest Physicians (ACCP) guidelines were recommended prescription for patients with PE of direct factor Xa inhibitors (dabigatran, rivaroxaban etc.) because they are preferable over vitamin K antagonist therapy as first 3 months after PE episode for no cancer patients. But in case of inability for patient to receive direct factor Xa inhibitors or vitamin K antagonist, aspirin is recommended over no aspirin to prevent recurrent PE in patients who are stopping anticoagulant therapy after hospital discharge and do not have a contraindication to aspirin [11], which is more applicable for our patient due to his low adherence to therapy and coast of Xa factor inhibitors in Ukraine for long-term therapy.

CONCLUSIONS

Not every case in medical practice are clearly understandable from the first view, but in the case of diagnostic difficulties, attention should be paid to the possible presence of the main risk factors for thromboembolic complications, the auscultators pattern in the lungs, and the possibility of developing PE (usage of widely unknown prognostic scales makes the task of physician easier and diagnosis evaluation more clear) in each clinical case.

REFERENCES

1. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism, updated / [S. V. Konstantinides, A. Torbicki, G. Agnelli, et al.] // Eur Heart J. – 2015. – № 36 (39). – P. 2642.
2. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding / I. M. Lang, R. Pesavento, D. Bonderman, J. X. Yuan // Eur Respir J. – 2013. – № 41 (2). – P. 462–468.
3. Wilbur J. Diagnosis of Deep Venous Thrombosis and Pulmonary Embolism Am Fam Physician / J. Wilbur, B. Shian // Am Fam Physician. – 2012. – № 86 (10). – P. 913–919.
4. Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians / [A. Qaseem, V. Snow, P. Barry, E. R. Hornbake, et al.] // Ann Fam Med. – 2007. – № 5 (1). – P.57–62.
5. Jorge A. Brenes-Salazar Westermark's and Palla's signs in acute and chronic pulmonary embolism: Still valid in the current computed tomography era / A. Jorge // J Emerg Trauma Shock. – 2014. – № 7 (1). – P. 57–58.
6. ACR Appropriateness Criteria® acute chest pain--suspected pulmonary embolism / [M. A. Bettmann, S. G. Baginski, R. D. White, P. K. Woodard, et al.] // J Thorac Imaging. – 2012. – № 27 (2). – P.28–31.
7. Cummings K. W .Multidetector computed tomographic pulmonary angiography: beyond acute pulmonary embolism / K. W. Cummings, S. Bhalla // Radiol Clin North Am. – 2010. – № 8 (1). – P. 51–65.
8. Evaluation of Patients with Suspected Acute Pulmonary Embolism: Best Practice Advice from the Clinical Guidelines Committee of the American College of Physicians / [A. S. Raja, J. O. Greenberg, A. Qaseem, et al]. // Ann Intern Med. – 2015. – № 163 (9). – P.701–11.
9. Aspirin for preventing the recurrence of venous thromboembolism / [C. Becattini, G. Agnelli, A. chenone, et al.] // N Engl J Med. – 2012. – № 66 (21). – P. 1959–1967.
10. Association of persistent right ventricular dysfunction at hospital discharge after acute pulmonary embolism with recurrent thromboembolic events / [S. Grifoni, S. Vanni, S. Magazzini, et al.] // Arch Intern Med. – 2006. – № 66 (19). – P. 2151–2156.
11. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report / [C. Kearon, E. A. Akl, J. Ornelas, et al.] // Chest. – 2016. – № 149 (2). – P.315–52.

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EXTERNAL RESPIRATORY FUNCTION IN A PATIENT AFTER REMOVAL OF THE MIDDLE AND LOWER LOBES OF THE RIGHT LUNG DUE TOCONGENITAL BRONCHIECTASIS

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A clinicalcase offemale patientwith obstructive bronchitisafter right-sided bilobectomy due tocongenitalbronchiectasis which developed on the background of suspected genetic predisposition withclinical signs of respiratory failure, butwithout significant disorders by instrumental examination of the of external respiration function.

KEY WORDS: external respiration function, right-sided bilobectomy of the lungs, congenitalbronchiectasis

ФУНКЦІЯ ЗОВНІШНЬОГО ДИХАННЯ У ПАЦІЄНТКИ ПІСЛЯ ВИДАЛЕННЯ СЕРЕДНЬОЇ ТА НИЖНЬОЇ ДОЛЕЙ ПРАВОЇ ЛЕГЕНІ У ЗВ'ЯЗКУ ІЗ ВРОДЖЕНИМИ БРОНХОЕКТАЗАМИ

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Клінічний випадок пацієнтки з обструктивним бронхітом після правобічної білобектомііу зв'язку із вродженими бронхоектазами, що виникли на тлі підозрюваної генетичної схильності із клінічними ознаками дихальної недостатності, але без істотних порушень функції зовнішнього дихання при інструментальному обстеженні.

КЛЮЧОВІ СЛОВА: функція зовнішнього дихання, правобічна білобектомія легень, вроджені бронхоектази

ФУНКЦИЯ ВНЕШНЕГО ДЫХАНИЯ У ПАЦИЕНТКИ ПОСЛЕ УДАЛЕНИЯ СРЕДНЕЙ И НИЖНЕЙ ДОЛЕЙ ПРАВОГО ЛЕГКОГО ПО ПОВОДУ ВРОЖДЕННЫХ БРОНХОЄКТАЗОВ

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Клинический случай пациентки с обструктивным бронхитом после правосторонней билобэктомии в связи с врожденными бронхоэктазами, который развился на фоне предполагаемой генетической предрасположенности с клиническими признаками дыхательной недостаточности, но без существенных нарушений при инструментальном исследовании функции внешнего дыхания.

КЛЮЧЕВЫЕ СЛОВА: функция внешнего дыхания, правосторонняя билобэктомия легких, врожденные бронхоэктазы

INTRODUCTION

The function of external respiration refers to gas exchange between the air in theupper and lower respiratory tract. The task of breathing is to supply tissues with oxygen and remove carbon dioxide from the body [1].

To evaluate the function of external respiration, study of the volume and velocity characteristics, the following curves are used: the flow-volume curve of the forced exhalation (for evaluating the ventilatory function of the bronchi), the indices of Tiffno and Gensler determined the presence of signs of obstruction [2], restrictive disorders are detected by measuring the total lung capacity andresidual volume. The informativeness of the technique for determining bronchial resistance for the evaluation of bronchial obstructive syndrome is shown by scientists [3]. The proper values of

pulmonary volumes and indices of forced expiration and gradation of their changes are presented by R.F. Clement, E.A. Zilber [4].

One of the major causes of impaired function of external respiration is bronchoectatic lung disease that can lead to removalof part of the lungs, and occurs in 1.5 % of the population, most often in childhood. Bronchiectasis is defined as permanent dilatations of bronchi with destruction of the bronchial wall. Bronchiectasis was considered a morbid disease with a high mortality rate from respiratory failure and cor pulmonale [4]. The clinical picture varies greatly and may involve repeated respiratory infections alternating with asymptomatic periods or with chronic production of sputum. Bronchiectasis should be suspected especially when there has been no exposure to tobacco smoke [5].

Patients with bronchiectasis typically present with recurrent pulmonary infections, productive cough, bronchial suppuration and purulent bronchorrhea [1, 6]. Similar to our case, cough, purulent and fetid sputum and hemoptysis are the most common symptoms in other described cases [1, 6–8].The goals of surgical therapy for bronchiectasis are to improve the quality of life and to resolve complications. There is also consensus that, because bronchiectasis is a progressive disease, affected regions should be resected in a way that preserves uninvolved lung parenchyma, and early pulmonary resection while the disease is still localized is preferred [2–3, 5, 7–12]. Ultimately, a minimum of two lobes or six pulmonary segments must be spared to ensure adequate pulmonary function [1, 9, 13–15]. For successful surgery, Kutly and colleagues recommend that the operation should be performed in «dry period», complete resection of suspected areas by intraoperative examination that could not be determined by radiological examination to decrease relapse rates, and surgical treatment in childhood because the residual lung could still grow to fill the space left in the chest after resection [7]. There is growing clinical evidence of accelerated or «catch-up» lung growth in youngsters whose lung disease is no longer active. Surgical therapy in case bronchiectasisalso can lead change the function of external respiration.

This clinical case demonstrates the influence bilobectomy of the lungs in patient with congenitalbronchiectasis onthe function of external respiration to determine the compensatory capabilities of the lungs after lobectomy.

CLINICAL CASE

The patient C, a woman born in 1956, was admitted to the clinical base of internal medicine department in Railway Clinical Hospital № 1 of «HC» JSC «Ukrzaliznytsia» in December, 2016 with complaints of recurrent dry cough, shortness of breath, headache, dizziness, fatigue, weakness, decreased resistance to physical stress, high blood pressure periodically to 160/90 mm Hg.

HISTORY OF DISEASE

Patient notes recurrence of obstructive bronchitis since birth. At the age of 14 bronchoscopy was performed and showed right-sided bronchiectasis, year later – right-sided bilobectomy was held in connection with congenital bronchiectasis. Consequently, with a diagnosis of chronic bronchitis she was observed by the pulmonologist, during exacerbations – inpatient treatment at the hospital.

The patient didn't follow prescribed treatment, used drugs irregularly.

In December 2016, suffered a sore throat, running nose, cough and fever till 38,5 for 3 days. Further the above symptoms have joined. She was admitted to day hospital of policlinic 24 with diagnosis: chronic obstructive pulmonary disease (COPD). Chronic diffuse bronchitis in remission stage, condition after right-sided bilobectomy (1970) due to congenital bronchiectasis.

Patient received mucolytics (ambroxol), antiviral drugs (amizon).

ANAMNESIS VITAE

Infections, injuries, tuberculosis, sexually transmitted diseases were denied.

Hereditary diseases were not identified.

Allergic history is not burdened.

Smoking denies.

Uses chemical agents for cleaning house.

Family history of known or suspected bronchiectasis is negative.

PHYSICAL EXAMINATION

General condition is satisfactory, consciousness is clear, emotionally stable.Height – 168 cm, weight – 57 kg, BMI –

20.35 kg/m^2 (normal range for BMI – 18.5 to 24.9).

Skin is pale-pink, without any scars. Symmetrical mild shin pitting edema is present. Peripheral lymph nodes are not palpable, on palpation of the thyroid gland left lobe is palpated with elastic consistency, painless. Signs of eyelid retraction, periorbital edema, proptosis are absent.

Respiratory system: on percussion – resonance percussion sound above both lungs, pulmonary below scapula angles from both sides, on auscultation– decreased vesicular breathing, wheezing in inferior parts of both sides of lungs. RR= 20 /min.

Cardiovascular system: heart borders extended to the left on 4 cm of midclavicular line, HR =65bpm, regular. Ps= 65 bpm. No pulse deficiency. Auscultation of the heart - heart sounds heart tones are rhythmic, clear. BP dextr = 135/80 mm Hg, BP sin = 143/88 mm Hg, (on the background of antihypertensive therapy).

Gastrointestinal system: abdomen is symmetrical, soft, painless, no discrepancies of the abdominal muscles. No visible peristalsis. Liver edge is smooth, painless, palpated 1.5 cm below the costal arch. Spleen and pancreas are not palpable.

Pasternatskiy sign is negative on both sides. Urination is free, painless

REFERRAL DIAGNOSIS

Chronic bronchitis. Essential arterial hypertension. Heart failure. Autoimmune thyroiditis. Systemic atherosclerosis. Obesity.

RESULTS OF LABORATORY AND INSTRUMENTAL DIAGNOSIS

Complete blood count): normal.

Urinalysis: normal.

Biochemical analysis: all parameters within the normal range.

Thyroid-stimulating hormone (TSH): normal.

Fasting glucose test: normal.

Blood lipid spectrum: normal.

Spirometry: ventilation lung function is not impaired.

Electrocardiography (ECG) signs of left ventricular hypertrophy.

RECOMMENDATIONS FOR FURTHER EXAMINATION

Spirometry with bronchodilator test (during stable stage); blood gases (PaO2, PaCO2); sputum culture; α – Antitrypsin; T4, T3, Anti-TPO; biochemical blood test (liver (ALT, AST, AP) and renal function tests (BUN); coagulogram; blood electrolytes (K, Na); chest X-Ray; ultrasound of thyroid gland and abdomen; consultation of an endocrinologist; 24 h -ambulatory ECG monitoring.

CLINICAL DIAGNOSIS

Main: Chronic obstructive pulmonary disease (COPD).Chronic diffuses bronchitis in remission stage, condition after right-sided bilobectomy (1970) about congenital bronchiectasis. Pulmonary fibrosis.Essential arterial hypertension stage III, 2 grade.Hypertensive heart (LVH).Heart failure with preserved ejection fraction II FC, stage B.Systemic atherosclerosis (atherosclerosis of the aorta and aortic valves, dyslipidemia II atype after Fredrickson).Very high added total CV risk.

Comorbidity: Osteohondrosis of cervical spine in a stage of unstable remission.Deforming osteoarthritis with the lesions of the small joints of the feet, hands. Insufficiency of joint function 2st., Ro 1–2st. Postmenopausal osteoporosis.

Angiopathy of the retina in both eyes. Myopia initial stage.Autoimmune thyroiditis, diffuse goiter focal 1 degree.Euthyroidism (2015). Peptic ulcer of duodenum, state after upper gastrointestinal bleeding 2 st. (2002).

PATIENT'S MEDICAL TREATMENT FOR LAST 6 MONTH

Salbutamol 100 mcg (Ventolin inhaler) 3–4 time per day

Valsartan 80 mg per day (does not take regularly).

Atorvastatin 10 mg (does not take regularly).

Aspirin 75 mg per day.

OUR RECOMMENDED TREATMENT ACCORDING LAST GUIDELINES

Non-pharmacologic:recommendations to maintain healthy lifestyle, decrease sodium intake, lipid lowering diet, increase contains of milk and sea fish in diet, aerobic non strenuous exercises; infection control (flu vaccination, pneumococcal vaccination); pulmonology rehabilitation.

Treatment strategy:Tiotropium 18 mcg (Spiriva Handihaler) 1 time per day for a long time; Salbutamol 100 mcg(Ventolin Inhaler) 3–4 time and when necessary; Lisinopril 10 mg in

the morningunder blood pressure control;Aspirin 75 mg once daily continuously; Rosuvastatin 20 mg in the evening; Calcium carbonate 1000 mg with vitamin D 800 mg 1 time per day in winter season; repeatspirography after 3 months; repeat visit to pulmonologist, endocrinologist after 3 months; exacerbation:oxygen (target saturation of 88–92 %) or systemic corticosteroids (40 mg prednisone per day for 5 days).

PROGNOSIS

Prognosis for life–in case of not following doctor's prescriptions – non-satisfactory

The prognosis for recovery – an unfavorable

PREVENTION

Secondary prevention of exacerbations of COPD include lifestyle modification; flu vaccination; pneumococcal vaccination; good blood pressure control, decrease sodium intake, lipid lowering diet, aerobic non strenuous exercises; control of fluid balance and checkup for decompensation of heart failure; control of compliance to our medical recommendations.

DISCUSSION

According to recent studies patients with complete resection of a localized bronchiectasis had better outcomes than those with incomplete resection. Regarding symptoms, the results of surgery can be considered satisfactory. More than 84 % of patients had relieved their preoperative symptoms. These results are similar to other cases [1, 3, 7–8, 13–14, 16–17].

The extent of compensatory lung growth in humans following lobectomy is incompletely investigated; a number of long-term physiological studies suggest, however, that some degree of compensatory growth may occur, especially in children [18–21].

Our clinical case shows recovery of parameters of external respiration functionin patient after 40 yearswhich requires further control.

In addition, our patient needs correction of the treatment of AH and more accurate diagnosis (and treatment) of thyroid disorder and first of all, modification of the lifestyle and reconsideration of the regularity of taking medicines.

CONCLUSION

This article exhibits a case of congenital bronchiectasis with bilobectomyand the subsequent restoration of the function of external respiration.

Despite of compensatory possibilities of lungs of external respiration function is not enough for compensation of lost lung volume and the patient must be considered as a whole.

REFERENCES

1. Surgical management of bronchiectasis: analysis and short-term results in 238 patients [electronic resource] / Balkanli K, Genç O, Dakak M. [et al.] // Eur J CardiothoracSurg. – 2003. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/14583301.
2. Surgical treatment in bronchiectasis: analysis of 166 patients. [electronic resource] / Kutlay H, Cangir AK, Enön S [et al.] // Eur J CardiothoracSurg. – 2002. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/11932159.
3. Belov A. A. Informativnost of a technique of determination of bronchial resistance for an assessment of a bronkhoobstruktivny syndrome / Belov A. A. // In: Theses of the X national congress by diseases of respiratory organs. – 2000. – 314 p.
4. Clement RF. Functional diagnostic testing in pulmonology / Clement R. F. – SPb, 1993. – 101 p.
5. Diagnosis and treatment of bronchiectasis [electronic resource]. / Vendrell M, de Gracia J, Olveira C et al. // Spanish Society of Pneumology and Thoracic Surgery. ArchBronconeumol. – 2008. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/19007570.
6. Surgeryforbronchiectasis. [electronic resource] / PrietoD, BernardoJ, MatosMJetal. // EurJCardiothoracSurg. – 2001. – Access mode:https://www.ncbi.nlm.nih.gov/pubmed/11423268.
7. Deslauries J. Surgical treatment of bronchiectasis and broncholithiasis / Deslauries J, Goulet S, Franc B // Advanced therapy in thoracic surgery / Deslauries J, Goulet S, Franc B. – Hamilton: ON: Decker, 1998. – p. 300–9.
8. Seaton D. Bronchiectasis. // Crofton and Douglas's respiratory diseases. / – New Delhi: Oxford University Press, 2000. – № 5. – p. 794–808.

9. Surgical treatment of bronchiectasis in children. [electronic resource] / Otgün I, Karnak I, Tanyel FC [et al.] // J PediatrSurg. – 2004. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/15486899.
10. Surgical treatment of bronchiectasis in children. [electronic resource] / Otgün I, Karnak I, Tanyel FC [et al.] // J PediatrSurg. – 2004. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/15486899.
11. Non-cystic fibrosis bronchiectasis. [electronic resource] / Neves PC, Guerra M, Ponce P [et al.] // CardiovascThoracSurg. – 2011. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/21979982.
12. Bronchiectasis: results of surgical and conservative management. A review of 393 cases. [electronic resource] / Sanderson JM, Kennedy MC, Johnson MF [et al.] // Thorax. – 1974. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/4850830.
13. Surgical results in bronchiectasis: analysis of 149 patients. [electronic resource] / Stephen T, Thankachen R, Madhu AP [et al.] // Asian CardiovascThorac Ann. – 2007. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/17664200.
14. Surgery for bronchiectasis. [electronic resource] / De Dominicis F, Andréjak C, Monconduit J [et al.] // Rev PneumolClin. – 2012. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/22365413.
15. Surgical treatment of bronchiectasis: early and long-term results [electronic resource] / Giovannetti R, Alifano M, Stefani A [et al.] // Interact CardiovascThoracSurg. – 2008. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/18490366.
16. Resection of more than 10 lung segments. A 30-year survey of 30 bronchiectatic patients. [electronic resource] / Laros CD, Van den Bosch JM, Westermann CJ [et al.] // J ThoracCardiovascSurg. – 1988. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/3336225.
17. A long-term study assessing the factors influencing survival and morbidity in the surgical management of bronchiectasis. [electronic resource] / Sehitogullari A, Bilici S, Sayir F [et al.] // J CardiothoracSurg. – 2011. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/22152759.
18. Campbell DN. The changing spectrum of pulmonary operations in infants and children [electronic resource] / Campbell DN, Lilly JR // J ThoracCardiovascSurg. – 1982. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/7078237.
19. Treatment outcomes of adjuvant resectional surgery for nontuberculous mycobacterial lung disease. [electronic resource] / Kang HK, Park HY, Kim D [et al.] // BMC Infect Dis. – 2015. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/7078237.
20. The Feasibility of Thoracoscopic Resection in Bronchiectasis. [electronic resource] / The Baysungur V, Dogruyol T, Ocakcioglu I [et al.] // SurgLaparoscEndoscPercutanTech. – 2017. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/707823
21. Surgical treatment of bronchiectasis: A review of 20 years of experience [electronic resource] / Coutinho D, Fernandes P, Guerra M [et al.] // Rev Port Pneumol. – 2016. – Access mode: https://www.ncbi.nlm.nih.gov/pubmed/7078237.

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THE ROLE OF IRON DEFICIENCY ANEMIA IN PATIENTS WITH CHRONIC HEART FAILURE IN THE EXAMPLE OF A CLINICAL CASE

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Anemia is common comorbidity in patients with heart failure. In Europe one in two patients with chronic heart failure has iron deficiency. Iron deficiency anemia is associated with a worse prognosis in the heart failure patient population and is an independent risk-factor for mortality, poor exercise capacity and low quality of life.

KEY WORDS: anemia, comorbidity, iron deficiency, heart failure

РОЛЬ ЗАЛІЗОДЕФІЦИТНОЇ АНЕМІЇ У ПАЦІЄНТІВ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Анемія – найбільш поширений коморбідний стан у хворих з хронічною серцевою недостатністю. В Європі більш ніж у половини пацієнтів, які страждають на хронічну серцеву недостатність, діагностовано дефіцит заліза. Залізодефіцитна анемія пов'язана з гіршим прогнозом у хворих з хронічною серцевою недостатністю і є незалежним фактором ризику смертності, зниження толерантності до фізичних навантажень та зниження якості життя.

КЛЮЧОВІ СЛОВА: анемія, коморбідність, дефіцит заліза, серцева недостатність

РОЛЬ ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИИ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Анемия – наиболее частое коморбидное состояние у пациентов с хронической сердечной недостаточностью. В Европе, более чем у половины пациентов, страдающих хронической сердечной недостаточностью, диагностируют железодефицит. Железодефицитная анемия ассоциируется с худшим прогнозом у пациентов с хронической сердечной недостаточностью и является независимым фактором риска смертности, снижения толерантности к физическим нагрузкам и снижения качества жизни.

КЛЮЧЕВЫЕ СЛОВА: анемия, коморбидность, железодефицит, сердечная недостаточность

INTRODUCTION

Anemia has been frequently observed in patients with chronic heart failure (CHF) and has been associated with increased mortality [1–2]. Increased mortality as well as increased rates of hospital admissions and decreased quality of life or exercise tolerance increased attention from the medical societies around the world. Estimates of the prevalence of anemia in patients with CHF and low ejection fraction range widely from 4 % to 61 % [3–4].

Causes of anemia in patients with CHF, possibility of anemia contributing to more severe CHF, forms of anemia prevalent in CHF populations, recommended treatment to

improve anemia and the general condition of patients with CHF, as well as a Clinical Case demonstrating the role of anemia in the developing heart failure will be further discussed [5].

Anemia is the most common disorder of the blood, affecting about a quarter of the people globally. It is a reduction in the total amount of red blood cells (RBCs) in the blood [2]. Reduction in the number of RBCs transporting O2 and CO2 impairs the body's ability for gas exchange leading to even more detrimental effects starting from the nervous system to the other systems of the body [6–7].

Heart failure (HF), also known as congestive heart failure (CHF) occurs when the heart fails to pump blood at the rate needed by the body. HF is a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function [5–6]. More than 20 million people have HF worldwide with men having a higher incidence than women. In the year after diagnosis the risk of death is about 35 % after which it decreases to below 10 % each year.

Anemia now occupies an important place in our present understanding of the pathogenesis of heart failure. In Europe, one in two patients with CHF has iron deficiency (ID) [8]. ID is associated with a worse prognosis in the HF patient population and is an independent risk-factor for mortality, poor exercise capacity and low quality of life [9–10].

Anemia has been found to be more prevalent in heart failure patients with a higher NYHA functional classification, greater degree of renal dysfunction, advanced age, female sex, and African-American race. The relationship between anemia and CHF is mutual, the former produces or worsens the latter and vice versa [1–2].

Anemia depends nearly exclusively on hemorrhage, which sets in motion an integrated response with actions in different regions, which include vasoconstriction and thrombosis, fluid retention, stimulation of erythropoiesis, and vascular repair. All these as a result of the human adaptive mechanisms induced to maintain perfusion, O2 supply to tissues, but also to preserve volume [11]. As a consequence, left ventricular dilation and hypertrophy can occur, with the next result being the production or worsening of CHF [11–12].

Potential causes for anemia in heart failure patients are likely to be a multifactorial. Routine diagnostic evaluation includes:

– complete blood count with reticulocyte count and index serum iron and total iron binding capacity transferrin saturation ferritin serum B12 and folate,

– thyroid stimulating hormone fecal occult blood test red blood cell distribution width (RDW) is a numerical measure of the variability in the size of circulating erythrocytes, taken during a standard blood count test.

Ineffective erythropoiesis causes heterogeneity in erythrocytes size and a higher RDW. RDW has recently emerged as a new prognostic marker of HF, regardless of Hb levels [12].

CLINICAL CASE

Patient medical profile

Female Patient N., 58-y old, retired, resident of urban area, was admitted to the hospital on 14th of November 2016

Chief complaints

Patient complains of general weakness, palpitations, stabbing chest pain, without any radiation, that is relieved without medications, dyspnea during physical activity, absent at rest numbness of fingertips, attention deficit disorder.

History of present illness

These complaints were felt by Patient N. 1 year ago. Last exacerbation was 3 days ago, she didn't take any drugs. After consulting with the physician, she was thus admitted to the hospital (14.11.2016) for further observation and tests.

Past medical history

For over 5 years, Patient N. suffered from essential hypertension. Her therapist prescribed medications such as diuretics and B-blockers (name not specified), but she did not comply with the proper dosing and as such, her BP level was unstable (she recalled it rising up to 150–170/100 mm Hg). Patient N. also suffered from chronic gastritis since year 2000. Patient N. has had no history of viral hepatitis, Diabetes Mellitus. She also denied any history of easy bruisability, menorrhagia. No surgical history.

Family/social history

Patient's mother and sister suffer from essential hypertension. No family history of

anemia or any other hematologic disorder, no family history of kidney and liver diseases. Patient N. denied any illicit drug history, alcohol use, smoking and allergic reactions both to environmental factors and to drugs. She is married, has 2 children.

General examination

Vital signs: temperature $36,7C^0$; blood pressure (BP) – 150/80 mm Hg; heart rate(HR) – 82 beats per minute; respiratory rate(RR) 19 breaths per minute; height 160 cm; body weight 57 kg; body mass index(BMI) – 22,2 kg/m^2.

Physical examination

Elderly female, had correct orientation in space and surroundings, mild depressed. Skin was pale with the absence of rashes and hemorrhages. Mucous membranes were pale and wet. Tongue is clear and wet. Turgor and elasticity of the skin were decreased. There were koilonychias. Subcutaneous fat tissue is normal. There were no any chest variations and surgical incision sites. Edema of the lower limbs was observed (2+). Joints were normal, active and passive movements were painless. The rest general inspection was unremarkable.

Objective examination

Percussion of the lungs was normal. Heart borders extended to the left on 1,5 cm of midclavicular line. Heart sounds were decreased in all points of auscultation. It was observed an accentuation of S2 on aorta point. Systolic murmur was auscultated on the 1st point of the heart auscultation (apex of the heart). Auscultation of the lungs was normal. No abdominal bruits or rubs were observed. The kidneys were not palpable. Stool and urination were normal.

Laboratory and instrumental methods

Complete blood count: (16.11.2016) Hb – 40 g/l; RBCs – $1.6*10^{12}$ /l; WBCs – $3.9*10^9$ /l; Segmented neutrophils – 79 %; Lymphocytes – 16 %; ESR – 18 mm/h

Complete blood count: (22.11.2016) Hb – 55 g/l; RBCs – $2.2*10^{12}$ /l; WBCs – $4.2*10^9$ /l; Segmented neutrophils - 74%; Lymphocytes - 19%; ESR-17 mm/h

Complete blood count: (29.11.2016) Hb-70 g/l; RBCs – $2.4*10^{12}$ /l; WBCs-$4.1*10^9$ /l; Segmented neutrophils – 73 %; ESR – 17 mm/h

Conclusion: remarkable decrease in Hb, RBC indicated a severe form of anemia. An increase in segmented neutrophils could be a result of an infection or inflammation process. A slight decrease in lymphocytes was observed. The rest results were unremarkable.

Biochemical blood test (16.11.2016): AsAT – 0,59 U/l; AlAT – 0,7 U/l. All parameters except AsAT, AlAT were normal.

Blood lipid profile (16.11.2016): LDL – 127 mg/dL; HDL – 55mg/dL; Total cholesterol – 5.5 mmol/L; Triglycerides – 58 mg/dL. All parameters except LDL were normal. There was a slight increase in low density lipoprotein (LDL).

Biochemical blood test (17.11.2016): Serum iron – 2.3 mkmol/l; total iron-binding capacity (TIBC) – 35.7 mkmol/l; Transferrin saturation – 6.4 %; serum ferritin – 28 ng/mL; Vitamin B12 – 85 ng/L. There was no vitamin deficiency anemia. Remarkable decrease in iron levels in the blood indicated Iron deficiency (ID) anemia.

Urinalysis (16.11.2016) was normal.

Esophagogastroduodenoscopy (16.11.2016): The mucosa of the esophagus was normal. Gastric mucosa was reddened and swollen. The structure of the folds was not changed.

Abdominal ultrasound (19.11.2016): Liver and gallbladder was normal. The spleen was enlarged (size 133×60 mm (N – 110×60 mm)).

Chest X-Ray (21.11.2016): There were no infiltrative or local changes in the lung. The sinuses were without liquid. Left heart border displaced sinisterly, inferiorly and posteriorly. There was rounding of the cardiac apex.

ECG (21.11.2016): Sinus rhythm, regular. Heart rate – 82 bts/min. Left ventricular hypertrophy.

Heart echocardiography (22.11.2016): End-DV LV – 120 ml; End-SV LV – 34 ml; mitral valve – regurgitation I degree; posterior wall of the LV – 13 mm; interventricular septum – 12 mm; ejection fraction – 40 %. Concentric left ventricle hypertrophy, decreased ejection fraction.

Upper gastrointestinal tract radiography (23.11.2016): There were signs of gastritis.

Six Minute Walk Test (6MWT) (25.11.2016): Patient N. walked 425 feet in 6 minutes. The test result complied with functional class II chronic heart failure.

Final diagnosis

Main Disease: Iron deficiency anemia, stage 2, severe degree, mixed genesis

Concomitant Diseases: Essential arterial hypertension II stage 2^{nd} grade. Chronic heart failure (CHF) 2^{nd} class according to the NYHA classification with reduced ejection fraction, chronic gastritis (unspecified).

Hospital treatment

RBCs transfusion BIII Rh+ 368,0 ml (16.11.16); tardyferon (ferrous sulfate) 80 mg 1 tablet twice a day; sufer 20 mg/ml IV; bisoprolol 2,5 mg 1 tablet once a day; perindopril 5 mg 1 tablet once a day.

Recommendation

1) Lifestyle modification.

Diet:

– Meat: beef, pork, or lamb, especially organ meats such as liver;

– Poultry: chicken, turkey, and duck, especially liver and dark meat;

– Fish, especially shellfish, sardines, and anchovies;

– Legumes, including lima beans, peas, pinto beans, and black-eyed peas;

– Iron-enriched pastas, grains, rice, and cereals.

Patients should be strictly warned against a «tea and toast diet» as tea strongly blocks iron absorption.

Activity restriction: patients with moderately severe iron deficiency anemia and significant cardiopulmonary disease should limit their activities until correction of the anemia with iron therapy.

2) Drug therapy: tardyferon (ferrous sulfate) 80 mg 1 tablet twice a day 3–4 months, perindopril 5 mg 1 tablet once a day.

CONCLUSIONS

The goal of this clinical case was to bring awareness to the prevalence of anemia and CHF, and influence of iron deficiency anemia in the progression of CHF while also focusing on diagnostic testing and treatment strategies [11].

The origins of anemia in heart failure are multifactorial. Its pathways are complex and not well understood.

There is no single treatment that will suit all patients, because of treatment must be based on an understanding of the causes of anemia in each patient.

According to last recommendation, the 2016 European Society of Cardiology guidelines, IV iron therapy is recommended for patients with Heart Failure with reduced Ejection Fraction and absolute or functional ID in order to alleviate HF symptoms and improve exercise capacity and quality of life [12].

The role of anemia in developing of HF should be researched and recognized more to understand the target levels of ferritin and iron in patients with or without anemia and CHF to reduce mortality and improve quality of life [13].

REFERENCES

1. Thomas D. S. Management of anemia in chronic heart failure / D. S. Thomas, A. S. Marc // Current opinion in Cardiology. – 2010. – № 25. – p. 154.
2. The anemia of heart failure / S. S. Donald, P. Alberto, L. Adrian, L. Doron // Acta Haematologica. – 2009. – No. 20. – p. 119.
3. Hempel E. The Evidence-Based Evaluation of Iron Deficiency Anemia / E. Hempel, E. Bollard // Med Clin North Am. – 2016. – № 5. – p. 75.
4. Living well with chronic heart failure [Electronic resource] // Heart Foundation. – 2014. – Access mode: http://www.medscape.com/cardiology.
5. Dickstein K. Guidelines for the diagnosis and treatment of acute and chronic heart failure / K. Dickstein, A. Cohen-Solal // Eur Heart J. – 2008. – № 29. – p. 2388.
6. Brugnara C. Hematologic aspects of kidney disease / C. Brugnara, K. Eckardt. – Philadelphia, 2011. – 2800 p. – (Taal MW, ed. Brenner and Rector's The Kidney).
7. Filippatos G. International registry to assess medical practice with longitudinal observation for Treatment of Heart Failure (REPORT-HF): rationale for and design of a global registry. / G. Filippatos, S. Khan, A. Ambrosy // Eur J Heart Fail. – 2015. – № 17. – p. 533.
8. Cohen-Solal A. High prevalence of iron deficiency in patients with acute decompensated heart failure / A. Cohen-Solal, T. Damy, S. Kerebel. // Eur J Heart Fail. – 2014. – № 16. – p. 789–91.
9. Nanas J. Etiology of anemia in patients with advanced heart failure / J. Nanas, C. Matsouka, D. Karageorgopoulos., 2006. – 2568 p.
10. Auerbach M. Single-dose intravenous iron for iron deficiency: a new paradigm. / M. Auerbach, T. Deloughery // Hematology Am Soc Hematol Educ Program. – 2016. – №. 57. – p. 234.
11. Dickstein K. Guidelines for the diagnosis and treatment of acute and chronic heart failure [Electronic resource] / K. Dickstein, A. Cohen-Solal, G. Filippatos // Eur Heart J. – 2008.

12. Anker S. D. Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency [Electronic resource] / S. D. Anker, C. J. Comin // N Engl J Med. – 2009.
13. Niehaus E. D. Repletion of Iron Stores With the Use of Oral Iron Supplementation in Patients With Systolic Heart Failure / E. D. Niehaus, R. Malhotra, D. Cocca-Spofford. // J Card Fail. – 2015. – №. 21. – p. 234–35.

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MULTIMORBID AND POLYPHARMACY IN CLINICAL CARDIOLOGY IN TERMS OF THE CLINICAL CASE

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In this article is raised the topic of multimorbidity and polypharmacy on the example of a clinical case with the main diagnosis of Ischemic Heart Disease: Systemic atherosclerosis with predominance of coronary arteries sclerosis. Stable angina class III. Hypertensive heart disease III stage 3rd degree. Aortocoronary bypass. Sick sinus syndrome, tachy-brady form. Constant form of atrial fibrillation-flutter. AV node catheter ablation with pacemaker implantation. Infarction pneumonia of the lingual segments of the upper lobe of the right lung. CHF II-B stage with preserved systolic function of the left ventricle (EF LV 53 %). Very high additional cardiovascular risk. Concomitant conditions: Chronic obstructive pulmonary disease: Chronic obstructive bronchitis 2 degrees severity. Chronic pulmonary insufficiency III degree. Obesity III degree. Diabetes mellitus type 2, medium severity, decompensated. Chronic renal failure, III stage. The ongoing therapy is discussed and recommendations are given to minimize it in order to avoid polypharmacy.

KEY WORDS: multimorbidity, cardiovascular diseases, drug therapy, polypharmacy

МУЛЬТИМОРБІДНІСТЬ І ПОЛІПРАГМАЗІЯ В КЛІНІЧНІЙ КАРДІОЛОГІЇ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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У статті розглянута тема мультиморбідності і поліпрагмазії на прикладі клінічного випадку з основним діагнозом Ішемічна хвороба серця: Системний атеросклероз з переважанням склерозу коронарних артерій. Стабільна стенокардія напруги III функціональний клас. Гіпертонічна хвороба III стадії 3 ступеня. Аортокоронарне шунтування. Синдром слабкості синусового вузла, тахі-браді форма. Постійна форма фібриляції-тріпотіння передсердь. Катетерная абляція АВ-з'єднання з імплантацією електрокардіостимулятора. Інфаркт-пневмонія язичкових сегментів верхньої частки правої легені. Хронічна серцева недостатність II-Б стадії зі збереженою систолічною функцією лівого шлуночка (ФВ ЛШ 53%). Дуже високий додатковий кардіоваскулярний ризик. Супутні стани: Хронічне обструктивне захворювання легень: Хронічний обструктивний бронхіт 2 ступеня тяжкості. Хронічна легенева недостатність III ст. Ожиріння III ст. Цукровий діабет 2 тип, середньої тяжкості, декомпенсований. Хронічна ниркова недостатність, III ст. Обговорюється що проводилася терапія і даються рекомендації щодо її мінімізації з метою уникнення поліпрагмазії.

КЛЮЧОВІ СЛОВА: мультиморбідність, серцево-судинні захворювання, лікарська терапія, поліпрагмазія

МУЛЬТИМОРБИДНОСТЬ И ПОЛИПРАГМАЗИЯ В КЛИНИЧЕСКОЙ КАРДИОЛОГИИ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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В статье поднята тема мультиморбидности и полипрагмазии на примере клинического случая с основным диагнозом ИБС: Системный атеросклероз с преобладанием склероза коронарных артерий. Стабильная стенокардия напряжения III функциональный класс. Гипертоническая болезнь III стадии 3 степени. Аорто-коронарное шунтирование. Синдром слабости синусового узла, тахи-бради форма. Постоянная форма фибрилляции-трепетания предсердий. Катетерная абляция АВ-соединения с имплантацией ЭКС. Инфаркт-пневмония язычковых сегментов верхней доли правого легкого. Хроническая сердечная недостаточность II-Б стадии с сохраненной систолической функцией левого желудочка (ФВ ЛЖ 53 %). Очень высокий дополнительный кардиоваскулярный риск. Сопутствующие состояния: Хроническое обструктивное заболевание легких: Хронический обструктивный бронхит 2 степени тяжести. Хроническая легочная недостаточность III ст. Ожирение III ст. Сахарный диабет 2 тип, средней тяжести, декомпенсированный. Хроническая почечная недостаточность, III ст. Обсуждается проводившаяся терапия и даются рекомендации по ее минимизации для избегания полипрагмазии.

КЛЮЧЕВЫЕ СЛОВА: мультиморбидность, сердечно-сосудистые заболевания, лекарственная терапия, полипрагмазия

INTRODUCTION

The topic of multimorbidity and progression of the cardiovascular pathology has been relevant and is being fully investigated [1–2]. The most frequent combinations of multimorbidity in clinical practice are Ischemic Heart Disease (IHD), Arterial Hypertension (AH), atherosclerotic dyscirculatory encephalopathy (ADE), atherosclerosis of mesenteric vessels, intestinal ischemia and other conditions [3–6].

Multimorbidity results in polypharmacy [7] that is when the number of medications simultaneously prescribed to the patient is significantly higher than the reasonable limits and when the probability and severity of their cumulative side effects are increasing catastrophically. In this regard, the physician is faced with the task of controlling prescriptions, the solution of which is not simple.

The clinical case demonstrates the problem and its possible solution.

CLINICAL CASE

57 year old man, resident of the city, transport retiree, disabled of the 2nd group.

COMPLAINTS

Patient E., born in 1959, was hospitalized with complaints on chest pains of a pressing character during moderate physical exertion, and at rest (go away at rest). These attacks are accompanied by dyspnea, palpitations. Feeling of suffocation at night. Shortness of breath decreases in the sitting position. Frequent remote dry wheezing. Transient increases in blood pressure to 230/130 mm Hg are accompanied by headache, dizziness. Dyspnea accretion while minimal physical exertion. Weakness. Fast fatigability.

ANAMNESIS

Hypertensive disease since 1984 with a maximum level of blood pressure of 230/130 mm Hg. The usual blood pressure of 140/90 mm Hg. In 2004, radiofrequency ablation and pacemaker implantation because of atrial fibrillation were performed. Subsequently, ablation was repeated twice. 22.10.2010, pacemaker reimplantation. 22.10.2010, the pacemaker was replaced to Baikal in the VVI mode due to depletion. In August 2011 patient suffered pulmonary embolism. 15.04.2013, coronary angiography was performed, multivessel lesion was revealed, and Coronary artery bypass grafting (CABG) was recommended. 23.10.2013, CABG – 2 shunts were performed. During the last 5 days, blood pressure began to increase more often, pain attacks increased and dyspnea became worse at rest. 11.09.2016 on the background of significance increases of blood pressure to 220/110 mm Hg the patient experienced severe shortness of breath, chest pain. Ambulance was called out, first aid was rendered, and patient was hospitalized in Kharkiv railway clinical hospital № 1 of the branch «Center of healthcare» of public JSC «Ukrainian Railway».

MEDICATIONS TAKEN:

Warfarin, Acetylsalicylic acid, Valsartan, Nifedipine, Rosuvastatin, Torasemide, Spironolactone, Dapagliflozin, Metformin, Nitroglycerin situationally in the presence of chest pains, Captopril / Nifedipine in case of

significance increase in blood pressure. There is indisputable presence of polipharmacy.

LABORATORY TESTS

Complete Blood Count: WBC count $7,5 \cdot 10^9$/L, band neutrophils 7 %, segmented 79 %, eosinophils 2 %, lymphocytes 10 %, monocytes 2 %, RBC count $4,2 \cdot 10^{12}$/L, platelet count $388 \cdot 10^9$/L, hemoglobin 122 g/L, hematocrit 39 %, ESR 27 mm/h, color index 0,87.

Chemistry Panel: glucose 13.52 μmol/L, urea 9.6 μmol/L, creatinine 119 μmol/L, total protein ratio g/L, AST 14 U/L, ALT 17 U/L, total bilirubin 5,2 μmol/L.

Coagulation Test: prothrombin complex according to Quique 78,1 %, soluble fibrin-monomer complexes 14 mg/100 mL, fibrinogen 3,77 g/L.

Urinalysis Test: color light yellow, clear, specific gravity 1010, pH 7,0, protein ratio 0,14 g/L, leukocyte 0–1, glucose – 24,12 mmol/L, ketone bodies were not detected.

Activity of serum enzymes: CK-83,6 U/L, CK-MB 16,47 U/L.

INSTRUMENTAL TESTS

ECG: Pacemaker rhythm with stimulation frequency = 65 beats / min on the background of atrial fibrillation, the form of the QRS complex is constant.

Echocardiography: Eccentric type of left ventricular hypertrophy. Sclerotic changes in the walls of the aorta, flaps of the aortic and mitral valves. Dilatation of all heart cavities. Left ventricular diastolic dysfunction type 2. Left ventricular myocardial contractility was reduced (Fractional shortening = 28 %, ejection fraction (EF) = 53 %).Tricuspid valve regurgitation of the 3rd-4th degrees, 1st degree regurgitation of the pulmonary artery valve, signs of the 1st degree pulmonary hypertension. Pacemaker electrode is fixed in the right heart cavities.

Ultrasonography of the lower extremities arteries: Atherosclerosis of the main arteries of lower extremities, occlusion of the left superficial femoral artery, multiple stenosis of the right superficial femoral artery up to 65 %

Chest X-ray: eED 0.3 mSv, focal and infiltrative changes in the lungs were not detected. The roots are structural, not enlarged. Sinuses are free. Aperture clearly delineated. The median shadow is widened in diameter; the heart is widened to the left. Pacemaker is on the left, dislocations and damages of the electrode were not revealed. Condition after sternotomy.

DIAGNOSIS

The underlying disease: Ischemic Heart Disease: Stable angina class III. Hypertensive heart disease III stage 3rd degree. Hypertensive heart (LVMH). Complicated hypertensive crisis (11.09.2016 Acute left ventricular failure: cardiac asthma). Atherosclerosis of coronary arteries (coronary angiography 15.04.2013). CABG – 2 shunts (23.10.2013). Sick sinus syndrome, tachy-brady form. Constant form of atrial fibrillation-flutter. AV node catheter ablation with pacemaker implantation (16.04.2004). Reoperation – AV node destruction (08.11.2004). Pacemaker reimplantation (22.10.10) in the VVI mode. The stimulation frequency 65. Pulmonary artery thromboembolism (16.08.2011). Infarction pneumonia of the lingual segments of the upper lobe of the right lung (2011). CHF II-B stage with preserved systolic function of the left ventricle (EF LV 53 %).

Very high additional cardiovascular risk.

Comorbid conditions: Cardio-cerebral syndrome on the background of vascular encephalopathy II stage. Cerebral athero-sclerosis. Chronic obstructive pulmonary disease: Chronic obstructive bronchitis 2 degrees severity. Chronic pulmonary insufficiency III degree. Metabolic syndrome. Obesity III degree. Diabetes mellitus type 2, medium severity, decompensated. Chronic renal failure, III stage. Urolithiasis, asymptomatic form. Mixed nephropathy. Obliterating atherosclerosis of the lower extremities arteries. Hemodynamically significant stenosis of the arteries of the lower extremities on both sides. Diabetic antipathy of the lower extremities. Chronic ischemia of the 2nd degree.

CLINICAL TREATMENT

Warfarin 3.75 mg at 5 pm, Valsartan 80 mg 2 times a day, morning and evening, Rosuvastatin 20 mg in the evening, Spironolactone 50 mg in the morning, Acetylsalicylic acid 75 mg in the evening, Nifedipine 40 mg, Torasemide 50 mg in the morning in a day, Metformin 500 mg 2 times a day, Aminophylline 2 % – 5.0 intravenously jet-like 2 times a day + Dexamethasone 8 mg + saline intravenously drip-like, Salmeterol 100 μg + Fluticasone 500 μg 2 times a day, Ipratropium bromide 40 μg + Fenoterol

hydrobromide 100 μg in case of threat of respiratory failure, Tiotropium bromide 22.5 μg once a day, soda 4 % - 200.0 intravenously drip-like.

RECOMMENDED REDUCED DRUG TREATMENT

Lisinopril 10 mg 2 times a day, Nebivolol 5 mg under the control of blood pressure and pulse, Nitrates as needed, Rivaroxaban 10 mg once a day, Rosuvastatin 10 mg once a day, Metformin 500 mg 2 times a day, Salbutamol 2 inhalations as needed, Salmeterol 25 μg 2 times a day.

CONCLUSIONS

Multimorbidity and polypharmacy take place in the clinical case. The solution of the problem is not simple, but the doctor should always monitor the prescribed combinations of drugs in order to minimize their number and choose the most suitable combination to get the best result with the least risk of side effects.

REFERENCES

1. Cardiovascular multimorbidity, emerging coalescence of the integrated panvascular approach [Electronic resource] / [P. Lanzer, H. Zühlke, P. Jehle et al.] // Z Kardiol. – 2004. – Access to resource: http://doi.org/10.1007/s00392-004-0062-8.
2. Multimorbidity and risk among patients with established cardiovascular disease: A cohort study [Electronic resource] / [L. G. Glynn, B. Buckley, D. Reddan, J. Newell, J. Hinde, S. F. Dinneen, et al.] // Br J Gen Pract. – 2008. – Access to resource: http://doi.org/10.3399/bjgp08X319459.
3. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany [Electronic resource] / [H. van den Bussche, D. Koller, T. Kolonko et al.] // BMC Public Health. – 2011. – Access to resource: http://doi.org/10.1186/1471-2458-11-101.
4. Vascular multimorbidity in patients with a documented coronary artery disease [Electronic resource] / [P. Lanzer] // Z Kardiol. – 2003. – Access to resource: http://doi.org/10.1007/s00392-003-0954-z.
5. Diagnosis and choice of the management strategy in patient with cardiac resynchronization therapy in case of chronic heart failure with multimorbidity / D. G. Drokin, I. V. Shanina, D. E. Volkov, A. O. Parfonova, N. V. Lysenko // The Journal of V. N. Karazin Kharkiv National University. Series: Medicine. – 2013. – № 1090, Issue 26. – P. 61–65.
6. Clinical case of persistent atrial flutter in patient with comorbid pathology / O. V. Gavrilyuk, Y. Y. Boeva, I. Ch. Anyasi, M. S. Maltseva, D. E. Volkov // The Journal of V. N. Karazin Kharkiv National University. Series: Medicine. – 2013. – № 1090, Issue 26. – P. 66–70.
7. Comorbidity study on type 2 diabetes mellitus using data minind / J. Korean, H. S. Kim, A. M. Shin [et al.] // Intern. Med. – 2012. – № 27 (2). – P. 197-202.

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HEART RATE VARIABILITY IN PAROXISMAL ATRIAL FIBRILLATION BEFORE AND AFTER CATHETER ABLATION AT AN EXAMPLE OF CLINICAL CASE

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Changes in heart rate variability (HRV) before and after catheter radiofrequency ablation (RFA) of pulmonary veins in paroxysmal atrial fibrillation (AF) are considered at an example of clinical case. Initially low HRV in patients after ablation halved, which can lead to increased frequency and extension of AF paroxysms. In the accompanied medication, which included bisoprolol, valsartan, atorvastatin and rivaroxaban, to increase HRV were proposed increasing the dose of bisoprolol or search for more effective beta blocker.

KEY WORDS: heart rate variability, catheter radiofrequency ablation, paroxysmal atrial fibrillation

ВАРІАБЕЛЬНІСТЬ СЕРЦЕВОГО РИТМУ ПРИ ПАРОКСИЗМАЛЬНІЙ ФІБРИЛЯЦІЇ ПЕРЕДСЕРДЬ ДО ТА ПІСЛЯ КАТЕТЕРНОЇ АБЛАЦІЇ НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ

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Зміни варіабельності серцевого ритму (ВСР) до та після виконання радіочастотної катетерної абляції (РЧА) легеневих вен при пароксизмальній фібриляції передсердь (ФП) розглядаються на прикладі клінічного випадку. Початково низька ВСР у пацієнтки після абляції знизилася вдвічі, що може призвести до збільшення частоти та подовження пароксизмів ФП. В медикаментозному супроводі, що включив бісопролол, валсартан, аторвастатин та рівароксабан, для збільшення ВСР запропоноване ступеневе збільшення дози бісопрололу або пошук більш дієвого бета блокатора.

КЛЮЧОВІ СЛОВА: варіабельність серцевого ритму, радіочастотна катетерна абляція, пароксизмальна фібриляція передсердь

ВАРИАБЕЛЬНОСТЬ СЕРДЕЧНОГО РИТМА ПРИ ПАРОКСИЗМАЛЬНОЙ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ ДО И ПОСЛЕ КАТЕТЕРНОЙ АБЛАЦИИ НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Изменения вариабельности сердечного ритма (ВСР) до и после выполнения катетерной радиочастотной аблации (РЧА) легочных вен при пароксизмальной фибрилляции предсердий (ФП) рассматриваются на примере клинического случая. Изначально низкая ВСР у пациентки после аблации снизилось вдвое, что может привести к увеличению частоты и удлинению пароксизмов ФП. В медикаментозном сопровождении, включавшем бисопролол, валсартан, аторвастатин и ривароксабан, для увеличения ВСС предложено ступенчатое увеличение дозы бисопролола или поиск более эффективного бета блокатора.

КЛЮЧЕВЫЕ СЛОВА: вариабельности сердечного ритма, катетерная радиочастотная аблация, пароксизмальная фибрилляция предсердий

INTRODUCTION

Atrial fibrillation (AF) represents a major cause of stroke, heart failure, sudden death and cardiovascular morbidity in the world. Whatever form it takes a risk of thromboembolic complications are equally high, so special attention should be given anticoagulant therapy for their prevention [1–6].

The strategy of patients management in case of paroxysmal AF is maintenance of sinus rhythm or transfer to permanent AF at obligatory minimization of thromboembolic complications risks. In some cases, antiarrhythmic therapy is contraindicated due to possible arrhythmogenic, organic toxic effects and threat of thromboembolic accidents, such patients should be offered radiofrequency ablation (RFA) [5].

Development and progression of paroxysmal AF affected by autonomic nervous system (ANS), firstly, drop the parasympathetic power level [7]. After RFA further reduction of HRV total power spectrum and violation ratio of its frequency components is observed [1, 4], which can lead to relapses and worsening of AF [7].

Existing research of HRV changes after RFA in patients with AF treated within 24 hours [1], while the ANS is rapidly changing process that may assess only a short record of a heart rate [7–8].

Given this, presented clinical case demonstrates changes of HRV before and after RFA in patients with paroxysmal AF, and allows predicting results of RFA.

OUR PATIENT

Woman 63 years, retired, city resident. The diagnosis on admission: ischemic heart disease (IHD), unstable angina (progressive tension). Condition after coronary ventriculography (CVG) and stenting (06.06.16). Atrial fibrillation, persistent form (10.18.16). Arterial hypertension (AH) III st., 3 deg. Heart failure II-a st. with preserved left ventricular (LV) ejection fraction. Risk IV (very high).

COMPLAINTS

Heartbeat and feeling of heart outages, that stops during one day after taking

450 mg propafenone. Burning pain in the heart, that irradiates the left arm, and disappears after taking 1–2 doses of nitroglycerin during 3 minutes. Shortness of breath with little exertion. Headache in the occipital region associated with an increasing blood pressure (BP) up to 140/90 mm Hg. Recurring pain in the cervical spine, pain and numbness in both upper extremities.

ANAMNESIS MORBI

For many years the patient has been suffering from hypertension with a maximum elevation of BP to 180/100 mm Hg. Chronic IHD about 4 years. In November 2013 – complaints of palpitations and a feeling of heart outages, first emerged AF was diagnosed. She was treated by amiodarone under the scheme with recommendations for further management. Since May 2014 a tendency to increase the frequency of episodes of paroxysmal AF was observed. She didn't follow the recommended regimen; the drug was carried out «on request». In June 2016 stenting of the left descending coronary artery due to its 90 % occlusion was performed. There was pain in the left heart, but BP is not rise above 140/95 mm Hg. In connection with increasing of heart pain, CVG was repeated in September 2016 with satisfactory results. The same time ultrasound revealed presence of 10.7 mm node in the left thyroid gland (TG). Thyroid hormones were investigated – TSH – 0,23 mkMEd/ml, T4 – 28.9 pmol/l. Patient was consulted by endocrinologist, diagnosed of nodular hyperthyroidism, tiamazol therapy was prescribed by scheme. At this time, the frequency of AF episodes increases to daily attacks, their tolerance deteriorates, and therefore she appealed to the cardiac arrhythmias expert. RFA of pulmonary veins was recommended, which was appeared in October 28, 2016. Treatment before RFA: propafenone, valsartan, bisoprolol, lercanidipine, aspirin, clopidogrel, rivaroksaban.

ANAMNESIS VITAE

Has a satisfactory living conditions. By profession an engineer, working conditions associated with emotional stress frequently. She adheres diet with restricted intake of salt to 3 g/day. Bad habits denied. Allergic anamnesis is not burdened. Tuberculosis, viral hepatitis, diabetes, mental and venereal diseases, trauma and surgery denied. During life she marks acute respiratory infections (3–4 times a year). Heredity is burdened by disease cardiovascular system, such as IHD and AH.

OBJECTIVE STATUS

General condition is moderately satisfactory, consciousness is clear, situation is active. Proper body constitution, high nutrition, body mass index – 29.7 kg/m2. Skin and visible mucous membranes are clean, pale pink, cyanosis is not defined. Pastosity of lower extremities. Lymph nodes are available for palpation, not increased. The thyroid gland is not visually determined by palpation – node in the left lobe of about 1 cm. Painless, not soldered to surrounding tissues. Musculoskeletal system normal, moderate tenderness paravertebral points in the cervical spine. Respiratory system is without pathological changes. Cardiovascular system: arrhythmic heart activity, tones are muted, heart rate (HR) = 115 ≠ Ps, forked first tone, accent of II tone above the pulmonary artery, mild systolic murmur on aorta, BP in both upper extremities 120/80 mm Hg. Belly regular shape, slightly increased by developed subcutaneous fat. Superficial palpation is painless, no peritoneal signs. Liver increased by 1.5 cm, painless, its margin is smooth, rounded. Effleurage symptom in lumbar is painless.

PRELIMINARY DIAGNOSIS

Main: IHD, stable exertional angina, III FC. AH, III st., 3 deg., risk is very high. Nodular hyperthyroidism. Atrial fibrillation, paroxysmal form tachysystolic variant. HF IIA st., III FC.

Concomitant: cervical spine osteochondrosis with brachialgic and cephalgic syndromes. Overweight.

DIAGNOSTIC TESTS RESULTS

Clinical analysis of blood – relative lymphocytosis, urine – oxalatrium. Biochemical analysis of blood characterized by increased levels of transaminases and alkaline phosphatase. Increased levels of free thyroxine (T4 free) were determined in the study of thyroid hormones. Chest X-ray revealed signs of hypertrophy and initial LV dilatation, hardening and calcinosis of aorta. Attack of paroxysmal AF was recorded by electro-cardiography (ECG) before RFA, presence of tachysystolic form of AF with HR=106, LV hypertrophy, disturbance of repolarization, systolic LV overload were shown, recorded HRV reflected higher spectrum total power (TP) with a predominance of low-frequency part of the spectrum. The same study was performed on a background of sinus rhythm, before RFA. It was ECG signs of none complete left bundle branch block and HRV reflected monomodal distribution of R-R intervals and low HRV TP range with a predominance of low-frequency part of the spectrum. Echocardiography revealed moderate LV hypertrophy, mitral valve prolapse with mitral regurgitation 1–2 st., aortic regurgitation 2 st., EF= 61 . Complete pulmonary veins isolation was made during RFA. The analysis of HRV after that characterized monomodal distribution of R – R intervals and critical reduction of TP range with prevalence of its very low-frequency (VLF) component. Comparing data of HRV before and after RFA followed next results: a sharp decline TP 46 %, increase in VLF activity doubly. These changes indicate a strong neurocardiopathy.

CLINICAL DIAGNOSIS:

IHD, stable exertional angina FC III, post CVG and upper descending artery - segment of the left coronary artery stenting (06.06.16). Atherosclerotic cardiosclerosis, mitral and aortic regurgitation 2 st. AH III st., 3 deg., risk is very high. LV hypertrophy, none complete left bundle branch block. Nodular hyperthyroidism. CHA2DS2 -VASc 4 points, HAS-BLED – 2 points, EHRA III. Condition after pulmonary veins isolation RFA (28.10.16). HF IIA st., III FC with preserved LV ejection fraction. Oxalatrium. Osteo-chondrosis of the cervical spine.

In the hospital received treatment: enoxaparin, rivaroksaban, propafenone, bisoprolol, valsartan, clopidogrel, meloxicam.

OUR RECOMMENDATION:

Lifestyle modifications – changing the daily routine and diet. Cyclical breathing, which is achieved when walking, swimming, using metronome, etc. [9].

Drug therapy: bisoprolol 5 mg/day – dose titration under HR and parameters of HRV control (if not the growth of TP spectrum of HRV - increasing the dose or search for another beta blocker), valsartan 80 mg/day in the morning, atorvastatin 5 mg to sleep. rivaroksaban 20 mg. Local on cervical spine – nimesulide gel 3 times daily over 10 days. [5–7]

Re-execution of clinical and biochemical blood analysis, urinalysis, determination of thyroid hormones (T3, T4, TSH), electrolyte composition of blood (K, Na, Mg), ECG,

echocardiography dynamics, ultrasound of the thyroid gland and abdominal organs, consulting endocrinologist and a neurologist, clinical observation of HRV were recommended.

TELEPHONE VISITS

The patient lives far away from the Hospital; it makes it impossible for her physical visits. Communication was supported by telephone visits.

A month after the RFA marked decrease in the frequency of attacks of paroxysmal AF to 7 times per month; paroxysms were stopped after taking 600 mg propafenone.

Tiamazol didn't receive, a dose of bisoprolol increased up to 5 mg/day.

CONCLUSIONS

The initial low TP spectrum of HRV in patients after RFA reduced by half, which can lead to increased frequency and extension of paroxysmal AF [1–2, 4].

In the accompanied medication, which included bisoprolol, valsartan, atorvastatin and rivaroksaban, to increase HRV were proposed increasing of bisoprolol dose and with no results – search for another beta blocker.

EPILOGUE

By the time the article was completed during a telephone visit, the patient reported a new paroxysm of AF lasting for 4 days, that's were not stopped after taking usual dose of propafenone. Given the results of her HRV it is a forecasted results. It is recommended to add sotalol 80 mg twice daily. If paroxysm were not stopped, electrical cardioversion is indicated, after which the issue will be to transfer the patient to a permanent form of AF.

REFERENCES

1. Dinamika pokazateley variabelnosti serdechnogo ritma do i posle radiochastotnoy ablatsii legochnyih ven i levogo predserdiya u patsientov s fibrillyatsiey predserdiy/ N. V. Sichinava [et al.]// Annalyi aritmologii. – 2009. – № 2.-P.63–73
2. Martimyanova L. A. General cardiovascular risk and the clinical condition of patients with atrial fibrillation / Martimyanova L. A. // The Journal of V. N. Karazin Kharkiv National University. Series «Medicine». – 2015. –- 1154 (Issue 29). – P. 45–48
3. Yabluchanskiy M. I. Internal diseases: the time of global somatic risk. / M. I. Yabluchanskiy, A. M. Yabluchanskiy, O. Y. Bychkova [et al.] // The Journal of V. N. Karazin Kharkiv National University. Series «Medicine». – 2013. – 1044 (Issue 25). – P. 5–7.
4. Long-term changes in heart rate variability after radiofrequency catheter ablation for atrial fibrillation: 1-year follow-up study with irrigation tip catheter. / Kang KW [et al.]//Journal of Cardiovasc Electrophysiology. – 2014. – № 25(7). – P. 693–700.
5. Sychev O. S. Fibrillyatsiya predserdiy. Sovremennyie podhodyi k lecheniyu i profilaktike oslozhneniy u patsientov s soputstvuyuschey patologiey serdtsa/ Sychev O. S. // Ukrainskiy meditsinskiy zhurnal – 2011. – 6 (86) XI–XII.
6. 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) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO)// European Heart Journal. – 2016. – P. 90.
7. Yabluchanskiy N. I. Heart rate variability for the practitioner [electronic resource] / N. I. Yabluchanskiy, A. V. Martynenko // Access mode: http://dspace.univer.kharkov.ua/handle/123456789/1462.
8. Heart rate variability. Standards of Measurement, Physiological Interpretation and Clinical Use. – Circulation. – 1996. – № 93. p. 43–65.
9. Implementation of biofeedback in a closed loop of heart rate variability and paced breathing in patient with arterial hypertension/ O. L. Kulik [et al.] // The Journal of V. N. Karazin Kharkiv National University. Series «Medicine». – 2014. – 1108 (Issue 27). – P. 10–15.

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HEART FAILURE IN THE PATIENT WITH ACROSSED INFECTIOUS ENDOCARDITI ON THE CONGENITAL BIKUSPIDAL VALVE OF AORTA

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Heart failure is a common cause of high mortality of patients all over the world. Arising on a background of complicated tonsillitis in patients with congenital heart diseases that significantly impairs the quality of life of patients and worsens the prognosis. Radical remains combined treatment of the patient with the elimination of complications.

For example, with clinical case report demonstrates and discusses the results of surgical and therapeutic treatment of heart failure with complications in the early postoperative period in a patient with congenital heart disease (bicuspid aortic valve).

KEY WORDS: valve replacement, heart failure, congenital heart disease

СЕРЦЕВА НЕДОСТАТНІСТЬ У ПАЦІЄНТА З ПЕРЕНЕСЕНИМ ІНФЕКЦІЙНИМ ЕНДОКАРДИТОМ НА ВРОДЖЕНОМУ БІКУСПІДАЛЬНОМУ КЛАПАНІ АОРТИ

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Серцева недостатність є частою причиною високої смертності пацієнтів у всьому світі. Виникає на тлі ускладнених тонзилітів у пацієнтів з вродженими пороками серця, що значно порушує якість життя пацієнтів і погіршує прогноз. Радикальним залишається комбіноване лікування пацієнта з усуненням виниклих ускладнень.

На прикладі клінічного випадку демонструються та обговорюються результати хірургічного та терапевтичного лікування серцевої недостатності з розвитком ускладнень в ранньому післяопераційному періоді у пацієнтів з вродженою вадою серця (бикуспідальним аортальним клапаном).

КЛЮЧОВІ СЛОВА: протезування клапана, серцева недостатність, вроджений порок серця

СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ У ПАЦИЕНТА С ПЕРЕНЕСЕННЫМ ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ НА ВРОЖДЕННОМ БИКУСПИДАЛЬНОМ КЛАПАНЕ АОРТЫ

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Сердечная недостаточность является частой причиной высокой смертности пациентов во всем мире. Возникает на фоне осложненных тонзиллитов у пациентов с врожденными пороками сердца, что значительно нарушает качество жизни пациентов и ухудшает прогноз. Радикальным остается комбинированное лечение пациента с устранением возникших осложнений.

На примере клинического случая демонстрируются и обсуждаются результаты хирургического и терапевтического лечения сердечной недостаточности с развитием осложнений в раннем постоперационном периоде у пациента с врожденным пороком сердца (бикуспидальным аортальным клапаном).

КЛЮЧЕВЫЕ СЛОВА: протезирование клапана, сердечная недостаточность, врожденный порок сердца

INTRODUCTION

Chronic heart failure (CHF) is an abnormality of cardiac structure and/or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures) [1].

One of the reasons for the development of heart failure in patients with prosthetic valves is transferred bacterial endocarditis, including on congenital heart defects (such as bicuspid aortic valve).

Even in the event of a delay in seeking surgical treatment, this tactic is optimal for the stabilization stage heart failure and to prevent progression of the disease [2–3].

The need for surgical treatment, we demonstrated on the example of clinical case.

OUR PATIENT

29 years old men, pensioner, IT spesialist, city resident. Date of admission: 19 – September – 2016.

COMPLAINS

Fatigue, dyspnea (paroxysmal nocturnal dyspnea (PND)), tachycardia, dizziness, swelling of lower limbs.

ANAMNESIS MORBI

In December 2012, suffered a sore throat, occurred for the first time. He was admitted to Institution of general and urgent surgery V.T. Zaycev NAMS of Ukraine in February 2013 for diagnosis of CHD: Infective endocarditis of the aortic valve, acute phase. Septicaemia (Str.pneumoniae). AV insufficiency III degree. MV insufficiency II degree. Congenital bicuspid aortic valve. HF IIB st., II FC. Patient received treatment with a course of antibiotics. He was offered surgical treatment which he at that moment refused. After discharge, the patient's condition began to deteriorate, growing signs of heart failure.

September 15th 2014 he was admitted in Kiev Heart Institute. September 22th 2014 – valvular replacement. Aortic (St. Jude #25) and mitral (St. Jude #29) valves. Was transferred from the intensive care with a temporary pacemaker. In the early postoperative period: frequent paroxysms of atrial flutter, frequent episodes of AV-block III degree, one episode of asystole with resuscitation. Oktober 13th 2014 – pacemaker implantation (St. Jude Verity DC (DDD)).

Results of echocardiography before surgery (15.04.2014): Aortic valve: bicuspid; cusps prolapse; hyperechogenic formation up to 5–8 mm. insufficiency +++, pressure gradient of 28 mm Hg. The diameter of the aorta 2.9 cm/4.2 cm/4.3 cm; aortic arch – 3.9 cm; Mitral valve: chords are sealed with visualized hyperechogenic formation, it is not excluded, the «old» calcifications of the growing season; insufficiency ++; EF=63 %.

Results of transesophageal echocardiography before surgery (17.09.14): Aortic valve: bicuspid; small hyperechogenic formations on wings AK, insufficiency +++; Mitral valve: signs of infectious endocarditis with the defeat of MV due to chronic trauma aortic insufficiency (small hyperechogenic vegetation, moving 3–4 mm; hyperechogenic, the conglomerate on chords of MV.

ANAMNESIS VITAE

In the early childhood was diagnosed with congenital heart disease. Bicuspid aortic valve. Complaints of fatigue, poor exercise capacity. Surgical treatment was deferred until reaching adulthood. Other infections, injuries, tuberculosis, sexually transmitted diseases were denied. Hereditary diseases are not identified.

Allergological history is not burdened.

OBJECTIVE STATUS

General condition – moderate grave, conciseness – clear, posture – active, body position – sitting on the chair. Patient can orientate himself in place, time, his personality. Height – 170 sm, weight – 102 kg, BMI – 35,29. Skin and mucosae are pink. Thyroid: no pathological changes. Skeleto-muscular system – deformity of the chest after sternotomy. BR – 20 /min. Lung percussion: pulmonary below scapula angles from both sides. Lung auscultation: decreased vesicular breathing wheezes inferial parts both sides. Borders of the heart: left border – outside of midclavicular left line on 4 cm. Heart auscultation: heart tones rhythmic, melody of mechanical valve on aortic and mitral valves. Pulse – rhythmic, 65 bts/min (during receiving blockers). BP 110/70 mm Hg. Abdomen: symmetric, increased in size due to subcutaneous fat. Liver: +l см. Spleen: normal. A sign of costovertebral angle tenderness is negative on both sides. Edemas: absent.

Varicose vein disease of lower extremities – absent. Feces: everyday, normal color.

PLAN OF SURVEY IN THE HOSPITAL

Clinical blood test (CBT) and urine analysis, kidneys and liver function tests, electrolytes, lipid profile, INR – international normalized ratio, electrocardiography (ECG), chest X-ray, echocardiography with doppler.

RESULTS

Clinical blood test: Normal test.
Urine analysis: Normal test.
Biochemistry test: Normal test.
Electrolytes: Normal test.
Lipid profile: Normal test.
INR: Normal test.
Electrocardiography: Left ventricular hypertrophy.

Chest x-ray: without pathological changes in the lungs. Pacemaker in left subcostal area, visible electrode to RV.

Heart ultrasound: Aortic valve: prosthesis, gradientpaint – 28/19 mm Hg. Mitral valve: prosthesis, pressure gradient – 19/10 mm Hg. Pericardium and pleural cavities without fluid. EF – 63 %.

Status after aortic and mitral valves replacement (prosthetic valves) (2014). The prosthesis is functioning correctly.

COMPLETE DIAGNOSIS OF OUR PATIENT

Mechanical prosthesis of aortic and mitral valves bileaflet type (22/09/2014) due to infective endocarditis of congenital bicuspid aortic valve (congenital heart disease) and mitral valve with predominance of insufficiency. Total AV-block III degree. Pacemaker statement St. Jude Verity DC (DDD) (13/10/2014). Total heart failure with preserved left ventricular pump function (ejection fraction = 63 %), C stage, II functional class by NYHA.

TREATMENT

Dietary sodium and fluid restrictions should be implemented in all patients with congestive heart failure. Limiting patients to 2 g/day of dietary sodium and 2 L/day of fluid will lessen congestion and decrease the need for diuretics.

Warfarin 5 mg 1 time/day, bisoprolol 10 mg 1 time/day, ramipril 2.5 mg 1 time/day, spironolactone 25 mg 1 time/day, torasemide 10 mg 1 time/per 5 days.

CONCLUSIONS

Infective endocarditis developed on the background of congenital heart disease (bicuspid aortic valve), which leaded to changes of heart chambers and caused heart failure. For compensation of heart failure we did surgical heart valve replacement. In the postoperative period such complication as complete AV block was developed, for treatment of which pacemaker was implanted. Thanks to a timely and comprehensive treatment, the patient is fully compensated.

REFERENCES

1. 2012 ESH/ESC Guidelines for the management of the diagnosis and treatment of acute and chronic heart: the task force for the diagnosis and treatment of acute and chronic heart failure of the Heart Failure Association (HFA) and the European Society of Cardiology(ESC) // European Heart Journal. – 2012. – Vol. 33, Is. 10. – P. 1787–1847.
2. 2012 ESH/ESC Guidelines for the management of valvular heart disease: The joint task force on the management of valvular heart disease of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of 12Cardiology (ESC) // European Heart Journal. – 2012. – Vol. 33, Is. 10. – P. 2451–2496.
3. Sharif B. J. R. The importance of timely treatment of the causes of heart failure on the example of the clinical case / B. J. R. Sharif, E. A. Liuta // The Journal of Kharkiv V. N. Karazin` National University, Series «Medicine». – 2016. – Issue 31 – P. 58–60.

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LONG-TERM OUTCOMES OF CATHETER ABLATION PULMONARY VEINS ON EXAMPLE OF A CLINICAL CASE PATIENT WITH PAROXYSMAL ATRIAL FIBRILLATION

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Catheter ablation of the pulmonary veins is the method of choice for the treatment of patients with symptomatic paroxysmal atrial fibrillation (AF). However, there are may be complications or recurrence of AF paroxysms and as we have described in our clinical case 2 after ablation really important to conclude that ablation does not eliminate drug therapy, but modifies it.

KEY WORDS: paroxysmal atrial fibrillation, catheter ablation, long-term outcomes, autonomic regulation

ВІДСТРОЧЕНІ РЕЗУЛЬТАТИ КАТЕТЕРНОЇ АБЛЯЦІЇ ЛЕГЕНЕВИХ ВЕН НА ПРИКЛАДІ КЛІНІЧНОГО ВИПАДКУ ПАЦІЄНТА З ПАРОКСИЗМАЛЬНОЮ ФОРМОЮ ФІБРИЛЯЦІЇ ПЕРЕДСЕРДЬ

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Катетерна абляція легеневих вен є методом вибору для лікування пацієнтів із симптоматичною пароксизмальною фібриляцією передсердь (ФП). Проте, можуть бути ускладнення чи рецидиви пароксизмів ФП і, як ми описали у нашому клінічному випадку 2 роки після абляції, дуже важливо зробити висновок про те, що абляція не скасовує медикаментозну терапію, але модифікує її.

КЛЮЧОВІ СЛОВА: пароксизмальна фібриляція передсердь, катетерна абляція, віддалені наслідки, вегетативна регуляція

ОТСРОЧЕННЫЕ РЕЗУЛЬТАТЫ КАТЕТЕРНОЙ АБЛЯЦИИ ЛЕГОЧНЫХ ВЕН НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ ПАЦИЕНТА С ПАРОКСИЗМАЛЬНОЙ ФОРМОЙ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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Катетерная абляция легочных вен является методом выбора для лечения пациентов с симптоматической пароксизмальной фибрилляцией предсердий (ФП). Тем не менее, могут быть осложнения или рецидивы пароксизмов ФП и, как мы описали в нашем клиническом случае 2 после абляции, очень важно сделать вывод о том, что абляция не отменяет медикаментозную терапию, но модифицирует ее.

КЛЮЧЕВЫЕ СЛОВА: пароксизмальная фибрилляция предсердий, катетерная абляция, отдаленные исходы, вегетативная регуляция

INTRODUCTION

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF, catheter ablation (CA) of AF has developed from a

specialized, experimental procedure into a common treatment to prevent recurrent AF. As first-line treatment for paroxysmal AF, randomized trials showed only modestly improved rhythm outcome with CA compared to antiarrhythmic drug therapy [1].

Complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter ablation, achievable by point-by-point radiofrequency ablation, linear lesions encircling the pulmonary veins. PVI was initially tested in patients with paroxysmal AF, but appears to be no inferior to more extensive ablation in persistent AF as well.

Antiarrhythmic drug therapy is commonly given for 8–12 weeks after ablation to reduce early recurrences of AF after catheter ablation, supported by a recent controlled trial where amiodarone halved early AF recurrences compared with placebo. Prospective studies have not been done, but a meta-analysis of the available (weak) evidence suggests slightly better prevention of recurrent AF in patients treated with antiarrhythmic drugs after catheter ablation.

Many patients are treated with antiarrhythmic drug therapy after catheter ablation (most often amiodarone or flecainide), and this seems a reasonable option in patients with recurrent AF after ablation [1–2].

The clinical case described below shows the long-term outcomes (2 years) of CA pulmonary veins of the patient with paroxysmal atrial fibrillation, which requires supportive medical therapy.

CLINICAL CASE

The patient S., a woman born in 1950, was admitted to the clinical base of internal medicine department in the Kharkiv city polyclinic #24 in October, 2016 with complaints of dyspnea during ordinary physical activity and absent at rest.

HISTORY OF DISEASE

Since 2000 autoimmune thyroiditis III degree with nodular goiter, euthyroid state; right-sided thyroidectomy and isthmus resection; according patient's report – euthyroidism all the time.

Since 2001hypertension with max level 220/110 mm Hg, usual BP 150/90 mm Hg on the background of drugs therapy.

In 2010 was paroxysmal tachycardia and palpitations, AF was first diagnosed. Since 2012 diagnosis: Paroxysmal atrial fibrillation, EHRA III. CHA2DS2-VASc – 2. HAS-BLED score – 2. Essential arterial hypertension stage II, 3 grade. hypertensive heart (LVH). Heart failure with preserved ejection fraction.

2014 – Catheter ablation of pulmonary veins.

After 3 days of ablation the patient had a paroxysm of AF – an electrical cardioversion was performed, continued to intake prescribed antiarrhythmic treatment for 3 months (betaxolol 10 mg/day, propafenon 300 mg/day). Despite of drug intaking, ones in 3 weeks she had episodes of AF which were being stopped by intaking additional 300 mg of propafenon.

After 3 months paroxysms of AF became more infrequent (once in 3 months) with shorter duration (1–2 hours), stopped after intaking propafenon 300 mg with mild/moderate symptoms of paroxysms of AF.

2015 – Gross hematuria on warfarin (the drug intaking was stopped); since 2015 – takes aspirin for prevention thromboembolic complications.

Following months (over 3) she notes poor control of BP (despite taking hypotension drugs).

After 8 months to the present day of CA she started suffer from paroxysmal tachycardia and heart palpitations with HR 120–130 bpm with mild symptoms, which are not related to physical exercise (mostly at night) 1 time per 2 months, sometimes related to incensement of blood pressure (BP) with duration from 1–2 min to 6 hours and converted to sinus rhythm by taking additional propafenon 300 mg and sometimes procainamide 500 mg.

ANAMNESIS VITAE

1981 – Appendectomy.

1993 – Acute pyelonephritis.

2004 – Radical hysterectomy, iatrogenic menopause.

2007 – Cyst in the right breast was removed.

PHYSICAL EXAMINATION

General condition is satisfactory, consciousness is clear, emotionally stable, optimistic mood. Height = 174 cm, weight = 105 kg, BMI = 34.68 kg/m^2, waist-to-hip ratio 1,07.

Skin is normal colored, without any scars. Peripheral lymph nodes, the thyroid gland are not palpable in the right side, slightly in the left.

Signs of eyelid retraction, periorbital edema, proptosis are absent.

Respiratory system: pulmonary percussion – resonant sound, auscultation – weakened vesicular breathing, no adventitious sounds.

Cardiovascular system: heart borders extended to the left on 1,5 cm of midclavicular line, HR =78 bpm, regular. Ps= 78 bpm. No pulse deficiency. Auscultation of the heart – heart sounds are muted, accent of the II tone above the aorta. Systolic murmur above the aorta. BP dextral = 150/90 mm Hg, BP sin = 175/100 mm Hg, (on the background of antihypertensive therapy).

Gastrointestinal system: abdomen is soft, painless, symmetrical, no discrepancies of the abdominal muscles. No visible peristalsis. Liver edge is smooth, painless, palpated 1.5 cm below the costal arch. Spleen and pancreas are not palpable. Symmetrical mild shin pitting edema.

REFERRAL DIAGNOSIS

Essential arterial hypertension. Paroxysmal atrial fibrillation. Heart failure. Autoimmune thyroiditis. Systemic atherosclerosis. Obesity.

RESULTS OF LABORATORY AND INSTRUMENTAL DIAGNOSIS

Complete blood count (16/10/2016): normal.

Urinalysis (16/10/2016): normal.

Biochemical analysis (16/10/2016): decreased kidney function (GFR by MDRD 54 ml/min/1.73 m2).

Thyroid-stimulating hormone (TSH) (16/10/16): normal.

Fasting glucose test (16/10/2016): normal.

Blood lipid spectrum (16/10/2016): II a type of dyslipidemia.

Electrocardiography (ECG) 2 years after CA: sinus rhythm, regular, heart rate 78 bpm, signs of left ventricular hypertrophy.

24 h -ambulatory ECG monitoring 2 years after CA: during the monitoring 22 h 38 min was registered sinus rhythm with a mean heart rate 74 bpm (maximum HR 120 pm, at 20:05:15, minimum HR 66 bpm – 16:50:55). Was recorded: single supraventricular premature contractions (total 266); single monomorphic ventricular premature contractions (total 49); short episodes of supraventricular tachyarrhythmia (total 4) with an average heart rate of 160 bpm with max duration for up to 5 seconds. Ischemic changes have not been identified. Circadian index 1.07 (N 1.24–1.44).

Heart rate variability (HRV) 2 years after CA: the character of the rhythmogram and HRV indicates the structure to stabilize the heart rhythm with the transition of its regulation from the reflex autonomic level to a lower humoral-metabolic, are not able to quickly provide homeostasis. Functional heart capabilities are reduced. Condition of a poor adaptation with a sharp decline in the functional capacity of the body.

Echocardiography 2 years after CA: atherosclerosis of aorta and aortic valves mild degree. Moderate dilatation of left atrium. Concentric left ventricle hypertrophy (LV Mass Index 100 g/m^2; RWT 0.49). Dyssynergic areas were not identified. Diastolic function – relaxation violation (E/A – 0.8).

RECOMMENDATIONS FOR FURTHER EXAMINATION

Repeat 24h – ECG monitoring in a month.

T4, T3, Anti-TPO.

Biochemical blood test (liver (ALT, AST, AP) and renal function tests (BUN), coagulogram.

Blood electrolytes (K, Na).

Chest X-Ray.

Ultrasound of thyroid gland and abdomen.

Consultation with an endocrinologist.

CLINICAL SYNDROMES

- Atherosclerosis (sclerotic changes of aorta and aortic valve).
- Arterial hypertension.
- Arrhythmias (paroxysmal AF).
- Reduction of circadian index and heart spectrum, as a manifestation of reducing humoral and autonomic regulation with non-dipper HR.
- Heart failure.
- Dyslipidemia.
- Hypertensive heart (LVH, atrial enlargement, diastolic dysfunction).
- Obesity.

CLINICAL DIAGNOSIS

Main:

Condition after CA of pulmonary veins due to paroxysmal AF (25/04/14), with decreasement in frequency of paroxysms from ones in 3 weeks to ones per 2 months.

EHRA II b.

CHA2DS2-VASc – 5, HAS-BLED score – 4.

Essential arterial hypertension stage II, 3 grade.

Hypertensive and arrhythmic heart (LVH, dilatation of LA).

Heart failure with preserved ejection fraction II FC, stage B.

Systemic atherosclerosis (atherosclerosis of the aorta and aortic valves, dyslipidemia II a type after Fredrickson).

Very high added total CV risk.

Autoimmune thyroiditis (focal? riedel's? hashimoto's?), condition after right – sided thyroidectomy and isthmus resection (2000), euthyroid.

Deep decline the power of all branches autonomic regulation: non-dipper HR with low degree of TP.

Comorbidity:

CKD 3a: hypertensive nephropathy (eGFR 54 ml/min/1.73 m2).

Obesity I class [3–4].

Non-alcoholic fatty liver disease?

PATIENT'S MEDICAL TREATMENT FOR LAST 6 MONTH

Bisoprolol 5 mg per day.

Propafenon 150 mg 2 times per day (without this drug –recurrence of AF paroxysms); during the paroxysms additionally 300 with/without procainamide 500 mg.

Valsartan 80 mg per day.

Atorvastatin 10 mg (do not intake regularly).

Aspirin 75 mg per day.

OUR RECOMMENDED TREATMENT ACCORDING LAST GUIDELINES

Lifestyle modification

1. DASH diet and regular physical activity lead to intensive weight reduction in addition to the management of other cardiovascular risk factors (in the range of 10–15 kg weight loss achieved), and to fewer AF recurrences and symptoms compared with an approach based on general advice in obese patients with AF [1].

2. Control of compliance to medical recommendations.

Drug treatment

1. B- blocker - CARVEDILOL 12,5 mg 2 times p/day (target HR – 60–65 b/m) under control of ECG.

2. AAD – PROPAFENONE 150 mg 3 times per day under control of ECG; additional 300 mg of propafenon in case of paroxysm of AF [5].

3. ARBs – VALSARTAN 160 mg in the morning.

4. Anticoagulant – RIVAROXABAN 15 mg p/day.

5. Statin-ROSUVASTATIN 20 mg in the evening.

6. Consulting with other subspecials to change treatment strategy (repeat catheter ablation?) [1].

PROGNOSIS

Prognosis for life – non-compliance to doctor's appointments – non-satisfactory.

The prognosis for recovery - an unfavorable.

PREVENTION

Secondary prevention of paroxysms of AF include lifestyle modification with weight reduction; good blood pressure control, because uncontrolled high blood pressure enhances the risk of stroke and bleeding events and may lead to recurrent AF; control of fluid balance and check up for decompensation of heart failure; control of compliance to our medical recommendations.

CONCLUSIONS

According to recent studies it has been demonstrated that pulmonary vein CA has favourable outcomes at 6–12 months post-ablation, but there are only few studies with a long-term follow-up and, as we see on our clinical case, after 2 years patient present with current deterioration of AF.

The vast majority of very longstanding paroxysmal/persistent AF patients maintained sinus rhythm at a mean follow-up time of 5 years following CA, associated with a significant improvement in symptom scores and, as we see on our clinical case, after 2 years patient maintained sinus rhythm, but with recurrence paroxysms of AF for last year with mild/moderate of symptom scores [6].

Often this procedure is not a radical solution of the problem, and most patients (as it also was shown on the example of our clinical case) are require adjunctive therapies including antiarrhythmics, DC cardioversions and re-ablation and upstream therapy (antihypertensive drugs and so on) [7].

Also our patient needs correction of the treatment of arterial hypertension and more properly diagnosis (and treatment) of thyroid disorder, and improvement the regulation at all levels - from the daily rhythm of the HR up to

relations in the activity of the vagal activity branches, first of all, interventions in the lifestyle and searching for the optimum time drug administration [8].

Of course, consider the presence of multiple syndromes on presented clinical case, we must not forget about the problem of polypharmacy and try to avoid it (many studies in ambulatory care define polypharmacy as a medication count of five or more medications, but it is practically impossible to investigate the biochemical compatibility in vivo of more than 4 drugs) [9–10].

REFERENCES

1. 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
2. Long-term outcomes after ablation of persistent atrial fibrillation: an observational study over 6 years / G.Wynn, M. El-Kadri, I. Haq, M. Das. // Open Heart. – 2016. - Vol. 3, Is. 2. - P. 1–10.
3. Estimated glomerular filtration rate reversal by blood pressure lowering in chronic kidney disease: Japan Multicenter Investigation for Cardiovascular DiseaseB CKD study / [Y. Yui, K. Kodama, A. Hirayama etc.]. // Journal of Clinical Hypertension. – 2012. – Vol. 15. – P. 171–175.
4. Mikhailidis D. The Role of Infection in Carotid Plaque Pathogenesis and Stability: The Clinical Evidence / Dimitri P. Mikhailidis. // Current Vascular Pharmacology. – 2010. – Vol. 8, Is. 6. – P. 861–872.
5. Stroobandt R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators / R. Stroobandt, B. Stiels, R. Hoebrechts. // American College of Cardiology. – 1997. – Vol. 79, Is. 4. – P. 418–423.
6. Lepillier A. A 5-year clinical follow-up after duty-cycled phased RF ablation of paroxysmal atrial fibrillation [Electronic source] / A. Lepillier, G. Lascault, O. Paziaud // Journal of interventional cardiac electrophysiology. – 2016. – Link: https://www.ncbi.nlm.nih.gov/pubmed/27878420.
7. Alcaraz R. Noninvasive time and frequency predictors of long-standing atrial fibrillation early recurrence after electrical cardioversion / R. Alcaraz, F. Hornero, J. Rieta. // North American Society of Pacing & Electrophysiology. – 2011. Vol. 34, Is. 10. – P. 1241–1250.
8. Golubkina E. O. Assessment of changes in the distribution ratios of ultra-low-frequency, low-frequency and highfrequency components of heart rate variability during the paced breathing test in patients with arterial hypertension / E. O. Golubkina // The Journal of V. N. Karazin Kharkiv National University, series «Medicine». – 2016. – Is. 31. – P. 10–17.
9. Cross-sectional investigation of drug-related problems among adults in a medical center outpatient clinic: application of virtual medicine records in the cloud [Electronic source] // Pharmacoepidemiology and drug safety. – 2016. – Link: https://www.ncbi.nlm.nih.gov/pubmed/27730699.
10. Polymorbidity does not determine polypharmacy / [A. I. Lakhonina, A. V. Filatova, N. V. Makienko etc.]. // The Journal of V. N. Karazin Kharkiv National University, series «Medicine». – 2015. – Is. 30. – P. 45–48.

Review

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LONG TERM EVOLUTION OF BONE RECONSTRUCTION WITH BONE GRAFT SUBSTITUTES

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The review involves clinical and experimental data, constitutive modeling, and computational investigations towards an understanding on how mechanical cyclic loads for long periods of time affect damage evolution in a reconstructed bone, as well as, lifetime reduction of bone graft substitutes after advanced core decompression. The outcome of the integrated model discussed in this paper will be how damage growth in femur after advanced core decompression subjected to mechanical cyclic loading under creep and fatigue conditions may be controlled in order to optimize design and processing of bone graft substitutes, and extend lifetime of bone substitutes.

KEY WORDS: advanced core decompression, bone graft substitute, damage, stress, creep, fatigue

ДОВГОСТРОКОВА ЕВОЛЮЦІЯ РЕКОНСТРУКЦІЇ КІСТОК ЗА ДОПОМОГОЮ КІСТКОВИХ ЗАМІННИКІВ – ІМПЛАНТАНТІВ

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Даний огляд включає клінічні та експериментальні дані, визначальні співвідношення, та обчислювальні дослідження, спрямовані на розуміння того як механічні циклічні навантаження протягом тривалих періодів часу впливають на зростання пошкоджуваності і скорочення довговічності імплантатів, що використовуються для компресійного заміщення дефекту кістки. У результаті моделювання, розглянутого в цій статті, буде встановлено як зростання пошкоджуваності протягом механічних циклічних навантажень в умовах повзучості та втоми імплантатів після компресійного заміщення дефекту стегнової кістки можна контролювати з метою оптимізації проектування та виготовлення кісткових замінників- імплантатів і збільшення терміну служби кісткових замінників.

КЛЮЧОВІ СЛОВА: компресійне заміщення дефекту кістки, кістковий замінник- імплантат, пошкоджуваність, напруга, повзучість, втома

ДОЛГОСРОЧНАЯ ЭВОЛЮЦИЯ РЕКОНСТРУКЦИИ КОСТЕЙ С ПОМОЩЬЮ КОСТНЫХ ЗАМЕНИТЕЛЕЙ – ИМПЛАНТАНТОВ

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Данный обзор включает клинические и экспериментальные данные, определяющие соотношения, и вычислительные исследования, направленные на понимание того как механические циклические нагрузки в течение длительных периодов времени влияют на рост повреждаемости и сокращение

долговечности имплантатов, используемых для компрессионного замещения дефекта кости. В результате моделирования, рассматриваемого в этой статье, будет установлено как рост повреждаемости вследствие механических циклических нагрузок в условиях ползучести и усталости имплантатов после компрессионного замещения дефекта бедренной кости можно контролировать с целью оптимизации проектирования и изготовления костных заменителей - имплантатов и увеличения срока службы костных заменителей.

КЛЮЧЕВЫЕ СЛОВА: компрессионное замещение дефекта кости, костный заменитель-имплантат, повреждаемость, напряжение, ползучесть, усталость

INTRODUCTION

Every year, over two million people worldwide sustain a bone grafting procedure to repair bone defects stemming from a disease or a traumatic event [1].

Core decompression represents an established technique for treatment of early stage osteonecrosis and most commonly used for disease that affects the hip joint. The procedure is designed to decrease pressure within the bone by restoring blood flow to the bone. For the first time, this procedure was popularized by Ficat and Arlet [2] in France in 1980. At present, this technique is one of the most commonly used surgical treatment options.

Core decompression consists of drilling one or more small channels with an 8–10 mm diameter into the necrotic lesion (dead bone) from the lateral subtrochanteric region of femur to remove an 8–10 mm core from the femoral head [3]. This is associated with a lack of structural support of the bone. Subtrochanteric stress fractures at the surgical entrance point of the core track were regularly described as a complication of conventional core decompression with a rate of about 1–2 % or even higher fracture rate [4]. That is why patients normally are requested to be partial weight bearing for several, normally six weeks due to the risk of fracture.

The so-called advanced core decompression is a modified technique of core decompression that may allow better removal of the necrotic tissue by using a new percutaneous expandable reamer, and refilling of the drill hole and the defect with the implantation of a bone graft substitute (Fig. 1) [3–4]. Such technique gives the possibility to reduce the risk of fracture after surgery.

Fig. 1. A proximal femur with the drilling canal and the bone defect filled by a bone graft substitute [4]

Practical recommendations related to the advanced core decompression are mainly based on clinical experience. So there is a need for rigorous studies to determine specific indications for this kind of treatment.

The finite element method has recently become a powerful technique for numerical simulation in the mechanics of femur. A three-dimensional finite element model derived from the reconstruction of core decompression or magnetic resonance (tomographic) images may help to effectively simulate the influences of core decompression on the mechanical behavior of femur.

The finite element studies concerning the advanced core decompression are given in [4]. The impact of the core decompression procedure and the surgical entrance point position on the stress distribution as well as on the fracture risk of the femur has been investigated. The effect of bone substitute stiffness on the biomechanical behavior of femoral bone after core decompression has been studied. Numerical results led to the conclusion that the success of advanced core decompression depends on the amount of necrotic tissue remaining in the femoral head after the procedure. Thus, modifications to the instrument are necessary to increase the amount of necrotic tissue that can be removed. Note also that all these studies are based on the linear elastic behavior of the femur and bone graft substitutes.

Different bone graft substitutes concerning the advanced core decompression have been used, such as a composite calcium sulphate ($CaSO_4$) – calcium phosphate ($CaPO_4$), tantalum or low-stiffness implants. The efficiency of these materials is still debated. One of alternative treatments is to use bioresorbable bone graft substitutes [1]. In this regard, the gradient elasticity theory was applied to study the effect of microstructure on remodeling of bones reconstructed with bioresorbable materials. In this way, one – [5], two – [1] and three – dimensional [6] biomechanical models of reconstructed bones have been considered.

Although the short term performance of femur after advanced core decompression is impressive, the long term performance is still unknown. Systematical studies related to the analyze the long term success and the long term risk of failure of bone graft substitute inside a femoral head after advanced core decompression have not been published so far.

The understanding of bone behaviors and functioning is a key in the ability to predict their evolutions and be able to make adequate diagnostics, surgeries and planning, and predict postoperation states [6].

Biomechanical degradation of femur after advanced core decompression can be related to the load and time dependent phenomena, such as damage, creep and fatigue. These phenomena in bone can be investigated experimentally.

OBJECTIVE

The specific objectives are: to specify the mechanisms of biomechanical degradation of femur after advanced core decompression subjected to mechanical cyclic loading; to develop the constitutive laws of biomechanical behavior and kinetic equations of damage (stiffness reduction, creep, fatigue) in femur after advanced core decompression considering the interaction between osteoblasts and osteoclasts combined with the mechanical response of bone, and taking into account nonlinear elastic deformation and creep under mechanical cyclic loading conditions, fatigue and ratcheting, receiving and healing damage, damage interactions between tension and compression; to identify biomechanical parameters in the proposed bone remodeling model using different experimental data for bone, bone graft substitutes and femur after advanced core decompression; to incorporate an integrated biomechanical constitutive model developed in this research into the ANSYS codes in a form of the computer-based structural modeling tool for analyzing bone density distributions over time, as well as, stress distributions over time in femur after advanced core decompression, for damage analysis and for lifetime predictions of bone graft substitutes; to calculate the time-dependent bone density distribution and time-dependent multiaxial stress distribution (finite element modeling, cell population dynamics, structural mechanics), and changes in damage at a discrete site of bone remodeling (continuum damage mechanics) in femur after advanced core decompression subjected to mechanical cyclic loading as a function of femur parameters, bone graft parameters, as well as, loading conditions, and additionally to predict the lifetime of bone graft substitutes; to find the relationship between bone cell architecture,

bone graft substitute, biological environment, loading conditions and degradation of femur over time after advanced core decompression (combination of 2, 3, 4 and 5); to compare the lifetime predictions obtained in this research against clinical and experimental data available for femur after core decompression in combination with bone substitutes.

MATERIALS AND METHODS

Bone damage. Mechanically, bone behaves identically to any other material in that it undergoes deformation and damage when subject to an external load. Bone sustains millions of loading cycles over the course of a lifetime and rarely breaks without a major traumatic event, and, thus, damage in bone is a naturally occurring event [7]. Damage is not detectable using clinical imaging modalities, but decreases bone's stiffness, strength, and toughness and eventually leads to collapse of whole bones [8].

There are three distinct varieties of damage in bone (Table 1), which can be identified as linear microcracks, diffuse microdamage, and microfractures. These types are distinguished by the way they form and their morphology; the nature of the stimuli that cause them to form, as well as, their location; and the manner in which they are repaired [7].

Table 1

Types of damage and their characteristics [7]

	Shape/ Dimensions	Stress mode	Tissue properties	Predominant location	Age	Repair
Linear Microcracks	Elliptical ~80 x 1 x300 μm	Compressive	More brittle	Interstitial	Older	Remodeling
Diffuse Microdamage	=<10 μm wide Unknown length	Tensile	More ductile	Within trabecular packets and osteons	Younger	Remodeling[1]
Microfractures	Complete fracture	Bending/shear	Off-axis orientation	Trabecular	Older	Endochondral ossification

Obviously that diffuse microdamage means microcracks on a lower length scale. Microcracks appear linear and spatially organized in 2D histological sections with a pertinent length of 10–70 μm [8]. In 3D, microcracks appear in approximately elliptical shape with an aspect ratio of 4:1 to 5:1. In histology studies, tensile microdamage appears to be more diffuse while compressive damage is rather expressed as linear microcrack. Thus, different damage development in tension and compression is a characteristic feature of bone.

Microfractures, on the other hand, are entirely different than the other forms of damage. Microfractures occur within cancellous bone and represent complete fractures of one or more trabeculae [7].

Also, damage interactions between tension and compression in bone have been considered [8-11].The mechanisms how bone damage is accumulated under different loading modes and coupled into another loading mode have been discussed. Impact of damage interactions on bone strength has been analyzed.

Damage reduces the bone’s future capacity to absorb energy prior to fracture, and in this sense deteriorates the mechanical properties of bone. However, the paradox of this is that the initiation and growth of microcracks in itself dissipates energy and delays a catastrophic complete fracture from occurring [7]. This presumes that the damage will be repaired in an efficient manner, before significantly more damage can be created [12]. This requires a signaling mechanism, and suggests a physiological role, not just a mechanical one, for bone damage [7, 13].

Creep. The consideration of the linear elastic deformation of femur after advanced core decompression is quite important in the structural analysis. However, this is not enough in order to understand the mechanisms of degradation of femur over time that affect essentially the lifetime reduction of bone graft substitute inside a femoral head.

It is known [14] that bones exhibit creep deformation considered as a time dependent irreversible deformation process. Both the tensile and compressive creep behaviors of cortical bone and trabecular bone are well documented [15–19]. They are characterized by creep strain versus time curves that have three distinct regimes (Fig. 2) (primary, secondary and tertiary) by analogy with the engineering

materials (steels, cast irons, light alloys) at high temperatures.

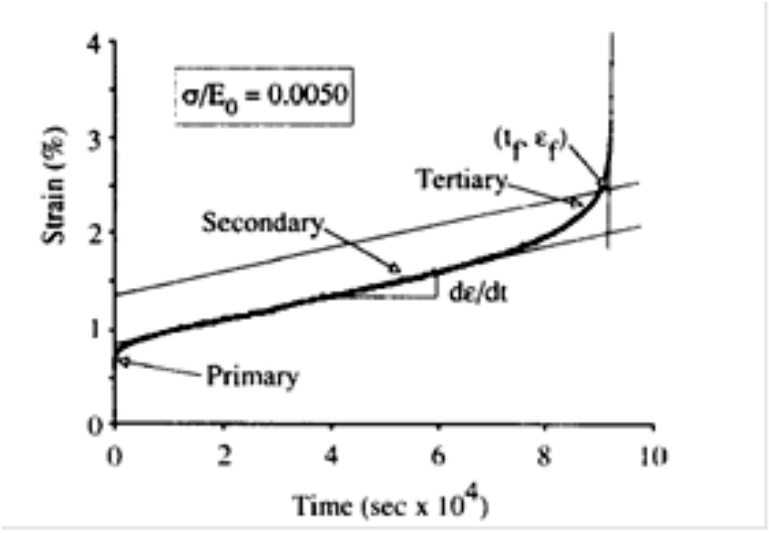

Fig. 2. Typical creep curve for trabecular bone with a time to failure of 25.5 h and a failure strain of 2.5 % [15]

Creep deformation changes the microstructure of bone by introducing microcracks (creep damage) in the final stage of the creep process. Furthermore, the velocity of the growth of already existing microcracks and of the nucleation of new ones essentially depends on the intensity of creep deformation. On the other hand, creep deformation of bone is influenced by the growth of microcracks. This influence begins at the primary and secondary stages of the creep process, and can be visible in the tertiary stage due to increase of the creep strain rate, preceding the creep rupture. The creep rupture case without increase in the creep strain rate can also be observed in bone. Thus, creep deformation and growth of creep damage in bone occur parallel to each other, and they have a reciprocal effect.

Figure 3 shows stress versus time to failure data in bone for tensile and compressive loading types under creep conditions. All specimens are normalized with Young's modulus. The experimental data are linear on a log-log plot which is similar to power law known for other materials.

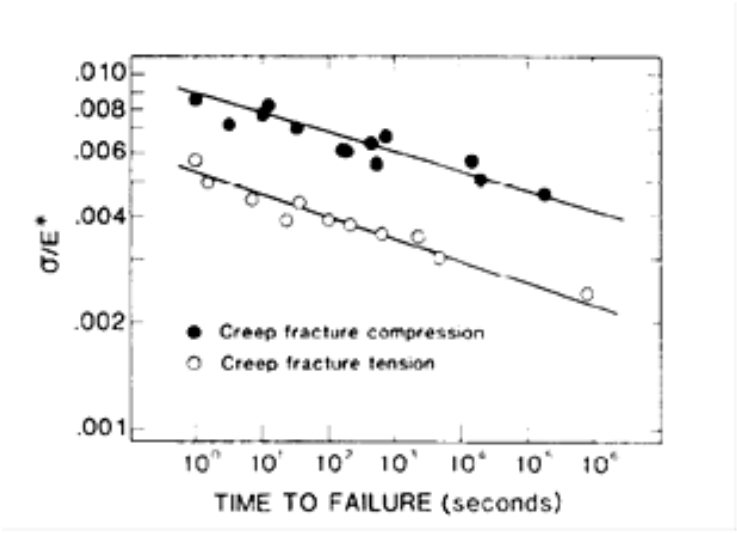

Fig. 3. Experimental creep ruptures data on human femoral cortical bone [20]

Now, a number of comments need to be made. First, creep curves obtained in bone from uniaxial tests under tensile and compressive loading types for one and the same absolute value of constant stress are essentially different and depend on the sign of the stress. This difference can be very large in the tertiary creep state due to the different creep damage growth in tension and compression. Thus, it is necessary to take into account the tension/ compression creep asymmetry of femur after advanced core decompression subjected to mechanical cyclic loading. Second, the creep and creep damage parameters of femur in the constitutive model should be a function of the bone density. Third, creep of composite calcium sulphate ($Ca\,S\,O_4$) – calcium phosphate ($Ca\,P\,O_4$) has been studied in [21].

Fatigue and ratcheting. Among various loading, cyclic loading (including axial, torsional and multiaxial load) plays an important role to damage bone [22]. Damage accumulation under cyclic loading is a major factor of failure in implants.

Fatigue data are extensively reported [22–25] for trabecular part and cortical part of bone. Also, it is found [26] the stiffness loss related to the damage growth in bone (Fig. 4) under cyclic loading. It is seen that stiffness loss under fatigue conditions is dependent on the type of loading.

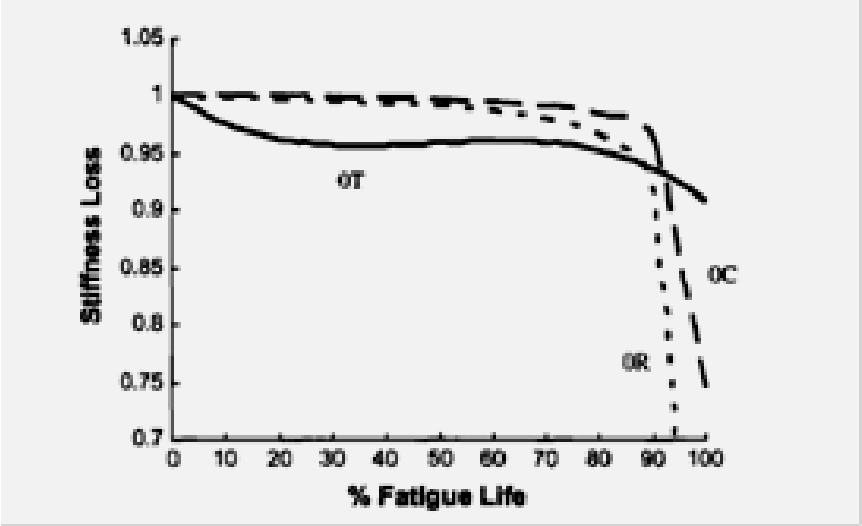

Fig. 4. Average stiffness loss profiles for specimens subjected to Zero-Tension (0T), Zero-Compression (0C) and zero-Torsion (0T) loading [26]

Fatigue damage in bone was identified as diffuse damage and linear microcracks using histological analysis [26]. Mode I fracture creates and propagates microcracks in the transverse direction for specimens subjected to Zero-Tension loading (Fig. 5). In contrast, the compressive group displayed Mode II cracking when crack surfaces slide over one another; damage is on a single plane (Fig. 5). Thus, there are differences in the kind of damage associated with fatigue in tension and compression.

Mode III fracture (Fig. 5) for specimens subjected to Zero-Torsion loading is similar to a tearing motion where the crack surfaces move relative to each other on multiple planes .

The fatigue life data for human femoral cortical bone [20] are presented in Fig. 6. Fatigue tests in specimens subjected to Zero-Tension and Zero-Compression loading were conducted at the two load frequencies (2 and 0.02 Hz). It is seen (Fig. 6) that fatigue lives of bone are longer in compression than in tension.

A comparison of the fatigue behavior of human trabecular and cortical bone tissue [24] was conducted under cyclic four-point bending (Fig. 7). The results show that trabecular specimens have significantly lower fatigue strength than cortical specimens, despite their higher mineral density values. Thus, the parameters of femur in the kinetic equation of fatigue damage should be a function of the bone density.

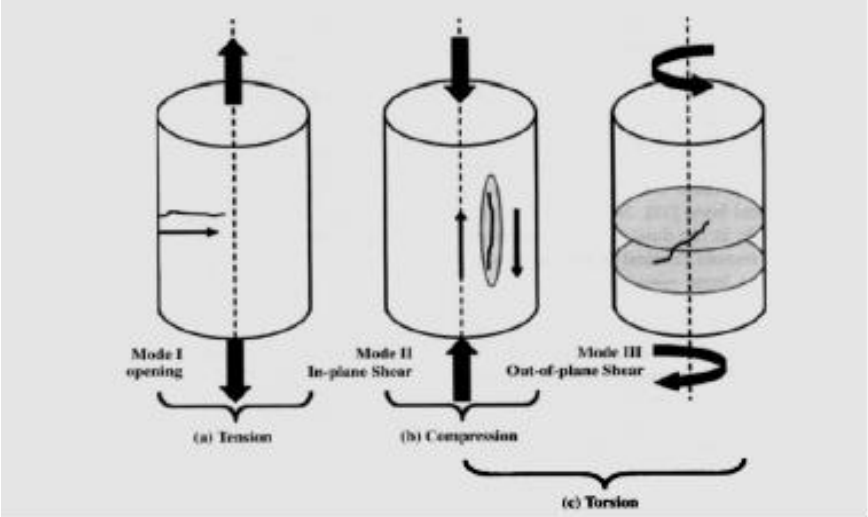

Fig. 5. Schematic representation of microcrack development in specimens subjected to Zero-Tension (Mode I) (a), Zero-Compression (Mode II) (b) and Zero-Torsion (Modes II and III) (c) loading [26]

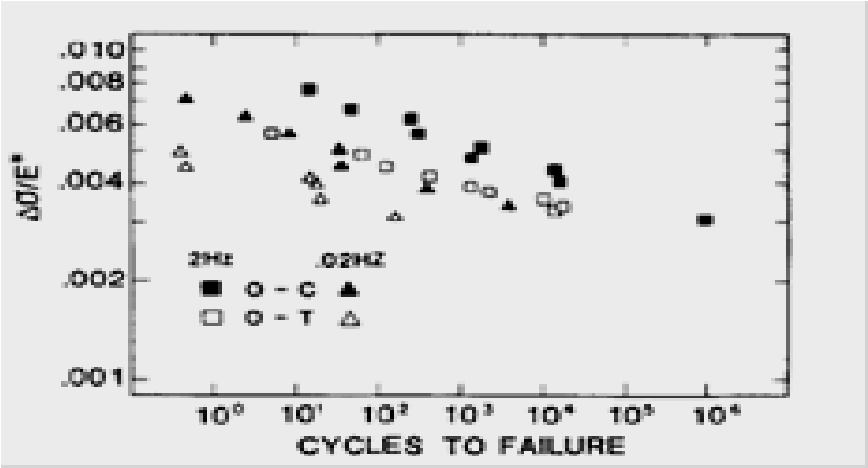

Fig. 6. Tensile (O-T) and compressive (O-C) cyclic loading data plotted as normalized stress versus cycles to failure [20]

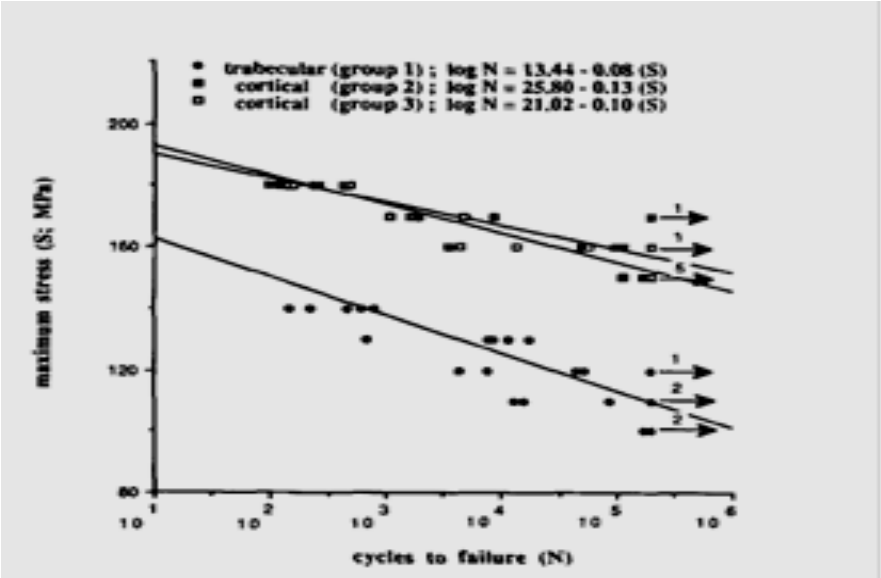

Fig. 7. Median S-N curves for each specimen group. The numbers on arrows indicate the number of run-out specimens for given stress levels [24]

Analysis of permanent strain during tensile fatigue of cortical bone (Fig. 8) shows that ratcheting occurs in cortical bone due to the cyclic softening of bone. Hence, ratcheting is considered as an irreversible deformation process dependent on the number of cycles.

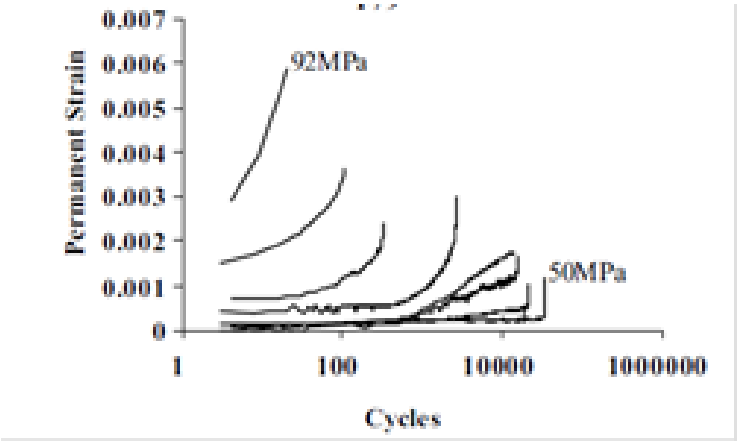

Fig. 8. Ratcheting strain in cortical bone as a function of the number of cycles for different levels of maximum stress [27]

Also, ratcheting was observed experimentally in trabecular bone for specimens subjected to Zero-Compression loading [28-30] and for samples subjected to a combination of torsion and compression fatigue [31]. Systematic studies of ratcheting during tensile, compressive, and shear fatigue of human cortical bone were conducted in [32].

Cell population dynamics model. Long term biomechanical adaptation is particularly significant to implant integration and stability in the postoperative state [33]. Wolff's law postulates [14] that bone can be remodeled based on the forces applied during its normal function, modifying its internal and external architecture and changing its shape and density. The remodeling phase of healing can continue for months or even years [34]. Biological cells continuously interact with and remodel the tissue in their immediate environment to establish a well-defined microstructural arrangement in healthy tissue. Local remodeling by cells becomes the crucial connecting point between the biological and mechanical fields [6, 34].

Various mathematical models of bone remodeling have been proposed in the literature [35]. In the present paper, the cell population dynamics model has been considered.

At the cellular scale, bone is composed of (i) bone matrix, infiltrated with minerals and with the osteocyte network; and (ii) vascular pores, containing soft tissues and cells [36]. Changes in bone microstructure occur by dissolution of old bone matrix by bone-resorbing cells (osteoclasts) and deposition of new bone matrix by bone-forming cells (osteoblasts). The bone remodeling process is governed by the interactions between osteoblasts and osteoclasts through the expression of several autocrine and paracrine factors that control bone cell populations and their relative rate of differentiation and proliferation [37].

The variation in bone density ρ at the remodeling site is expressed in terms of percentage of the initial mass depending on the number of osteoclasts and osteoblasts [37]:

$$\frac{d\rho}{dt} = k_2 X_B - k_1 X_C$$

Here k_1 and k_2 are the normalized activities, X_C and X_B are, respectively, the numbers of actively resorbing osteoclasts and forming osteoblasts at a remodeling site defined by Komarova et al. [38]:

$$\begin{cases} X_C = x_C - \bar{x}_C & if\ x_C > \bar{x}_C \\ X_C = 0 & if\ x_C \le \bar{x}_C \end{cases}$$

and

$$\begin{cases} X_B = x_B - \bar{x}_B & if\ x_B > \bar{x}_B \\ X_B = 0 & if\ x_B \le \bar{x}_B \end{cases}$$

where $\bar{x}_C$ and $\bar{x}_B$ are, respectively, the number of osteoclasts and osteoblasts at steady state. The system of differential equations describing the osteoclast and osteoblast rates and interactions using parameters, which characterize the autocrine and paracrine factors, can be expressed by [37]:

$$\begin{cases} \frac{dx_B}{dt} = \alpha_2 x_C^{g12} x_B^{g22} - \beta_2 x_B \\ \frac{dx_C}{dt} = \alpha_1 x_C^{g11} x_B^{g21} - \beta_1 x_C \end{cases}$$

where α_1 is the osteoclast production rate, β_1 is osteoclast removal rate, α_2 is the osteoblast production rate, β_2 is the osteoclast removal rate. Parameter $g11$ describes the combined effects of all the factors produced by osteoclasts that regulate osteoclast formation (osteoclast autocrine regulation). Parameter $g22$ describes the combined effects of all the factors produced by osteoblasts to regulate osteoblast formation (osteoblast autocrine regulation). Parameter $g12$ describes the combined effects of all the factors produced by osteoclasts that regulate osteoblast formation, such as TGFβ (osteoclast-derived paracrine regulation). Parameter $g21$ describes the combined effects of all the factors produced by osteoblasts that regulate osteoclast formation, such as OPG and RANKL (osteoblast-derived paracrine regulation). In this proposal, special attention is paid to the particular case, where a bone cell grows normally and only influences its neighbor's activity, but does not produce autocrine factors. Therefore, we can write [37].

$$\begin{cases} g11 = g22 = 0 \\ g12 = A_1 + B_1 e^{-\gamma_1 S(x,\,t)} \\ g21 = A_2 + B_2 e^{-\gamma_2 S(x,\,t)} \end{cases},$$

where A_1, B_1, A_2, B_2, γ_1, and γ_2 are model parameters that regulate the production of paracrine factors, $S(x, t)$ denotes the mechanical stimulus function. The mechanical stimulus used here is expressed in terms of strain energy density.

The bone adaptation approach given above allows for the computation of changes in density of femur after advanced core decompression at a discrete site of bone remodeling at a macroscopic scale. In order to simulate the remodeling process from a mechanobiological point of view, this approach needs to be implemented, for example, into an ANSYS code (considering bone density instead of temperature in the finite element model in Fig. 9).

Fig. 9. Finite element model of femur generated by ANSYS [4]

Structural mechanics model. The cell population dynamics model needs to be coupled to the structural mechanics model. Total strains in femur are assumed to be composed of nonlinear elastic part, part due to creep and ratcheting part accumulated during cycling loading.

The creep strain rates are related to the stresses under multiaxial loading as follows [39]:

$$\frac{\mathrm{d}\varepsilon_{kl}^c}{\mathrm{d}t} = \frac{\sigma_e^n}{(1-\phi)^m}\left(\frac{3}{2}\frac{As_{kl}}{\sigma_i} + C\delta_{kl}\right) \qquad (1),$$

where $\sigma_e = A\sigma_i + C\sigma_{kl}\delta_{kl}$, $\sigma_i = \sqrt{\frac{3}{2}s_{kl}s_{kl}}$, s_{kl} is the stress deviator, σ_{kl} is the stress tensor, t is time and A, C, n, m are material parameters. A continuum damage parameter by Kachanov-Rabotnov ϕ has been introduced into the creep law given by Eq. (1) with the formulation of the following creep damage growth equation

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \frac{\Sigma_e^k}{(1-\phi)^l} \qquad (2),$$

where $\Sigma_e = A_0\sigma_i + C_0\sigma_{kl}\delta_{kl}$, A_0, C_0, k and l are material parameters. Equations (1) and (2) reflect the tension/compression asymmetry of creep and creep damage in femur.

Also, description of ratcheting and fatigue damage in femur is considered. The components of the ratcheting strain tensor can be defined as follows [39]:

$$\dot{\varepsilon}_{kl}^{r} = \frac{\tau_e^p N^q}{(1-\varphi)^f}\left(\frac{3}{2}\frac{a\kappa_{kl}}{\tau_i} + c\delta_{kl}\right) \qquad (3),$$

where N is a number of cycles, $\tau_e = a\tau_i + c\tau_{kl}\delta_{kl}$, $\tau_i = \sqrt{\frac{3}{2}\kappa_{kl}\kappa_{kl}}$, κ_{kl} is the stress amplitude deviator during cycling , τ_{kl} is the tensor of the mean stresses during cycling, dot above the symbol denotes the derivative with respect to the number of cycles, and *a*, *c*, *p*, *q* and *f* are material parameters. Also, description of ratcheting and fatigue damage in femur is considered. The components of the ratcheting strain tensor can be defined as follows [39]:

$$\dot{\varepsilon}_{kl}^{r} = \frac{\tau_e^p N^q}{(1-\varphi)^f}\left(\frac{3}{2}\frac{a\kappa_{kl}}{\tau_i} + c\delta_{kl}\right) \qquad (3)$$

where $\rho_e = d\tau_i + e\tau_{kl}\delta_{kl}$, *d*, *e*, *x*, *b* and *v* are material parameters. Equations (3) and (4) reflect the tension/compression asymmetry of ratcheting and fatigue damage in femur.

Note that material parameters in Eqs. (1)-(4) are functions of bone density and bone mineralization, and can be identified from the basic experiments under tension and compression [40].

Diffusion model to describe osteogenesis within a porous $Ca\,P\,O_4$ scaffold needs to be considered. In this regard, the concentration of mesenchymal stem cells can be found using diffusion model developed in [41].

CONCLUSION

Analysis of bone density, stress and damage distributions over time in femur after advanced core decompression as well as lifetime prediction studies in this review are related to the consideration of the physically nonlinear initial/three-dimensional boundary value multiphysics problem. Therefore, commercial software package ANSYS needs to be used for structural analysis, computational modeling and simulation, when the integrated constitutive framework discussed in this paper will be implemented into its codes.

The lifetime predictions obtained in this research need to be compared against clinical and experimental data available for femur after core decompression in combination with bone substitutes.

The outcome will be how damage growth in femur after advanced core decompression subjected to mechanical cyclic loading under creep and fatigue conditions may be controlled in order to optimize design and processing of bone graft substitutes, and extend lifetime of bone substitutes.

PROSPECTS FOR FUTURE STUDIES

The new knowledge obtained in this research needs to be transferred to research communities related to advanced core decompression. Also, the young professionals training needs to be provided at the Arts et Métiers ParisTech, France, and at the V. N. Karazin Kharkiv National University, Ukraine, on how to use the computer-based structural modeling tool developed in this research.

REFERENCES

1. Madeo A., George D., Rémond Y. (2013). Second-gradient models accounting for some effects of microstructure on remodelling of bones reconstructed with bioresorbable materials. Computer methods in biomechanics and biomedical engineering, 16, 260–261.
2. Ficat R. P., Arlet J. (1980). Necrosis of the femoral head. In: Ischemia and Necrosis of Bone. Baltimore: Williams & Wilkins, 53–74.
3. Landgraeber S., Theysohn J. M., Classen T., Jäger M., Warwas S., Hohn H. P., Kowalczyk W. (2013). Advanced core decompression, a new treatment option of avascular necrosis of the femoral head–a first follow-up. Journal of tissue engineering and regenerative medicine, 7(11), 893–900.
4. Tran T. N., Kowalczyk W., Hohn H. P., Jäger M., Landgraeber S. (2016). Effect of the stiffness of bone substitutes on the biomechanical behaviour of femur for core decompression. Medical engineering & physics, 38(9), 911–916.
5. Madeo A., George D., Lekszycki T., Nierenberger M., Rémond Y. (2012). A second gradient continuum model accounting for some effects of micro-structure on reconstructed bone remodelling. Comptes Rendus Mécanique, 340(8), 575–589.

6. Scala I., Spingarn C., Rémond Y., Madeo A., George D. (2016). Mechanically-driven bone remodeling simulation: Application to LIPUS treated rat calvarial defects. Mathematics and Mechanics of Solids, 1081286516651473.
7. Burr D. B. (2011). Why bones bend but don't break. J Musculoskelet Neuronal Interact, 11(4), 270-285.
8. Mirzaali M. J., Bürki A., Schwiedrzik J., Zysset P. K., Wolfram U. (2015). Continuum damage interactions between tension and compression in osteonal bone. Journal of the mechanical behavior of biomedical materials, 49, 355–369.
9. Reilly, G. C., Currey, J. D. (1999). The development of microcracking and failure in bone depends on the loading mode to which it is adapted. Journal of Experimental Biology, 202(5), 543–552.
10. Wolfram, U., Schwiedrzik, J. (2016). Post-yield and failure properties of cortical bone. BoneKEy reports, 5. doi:10.1038/bonekey.2016.60
11. Zysset P. K., Schwiedrzik J., Wolfram U. (2016). A statistical damage model for bone tissue based on distinct compressive and tensile cracks. Journal of biomechanics, 49(15), 3616–3625.
12. Seref-Ferlengez Z., Kennedy O. D., Schaffler M. B. (2015). Bone microdamage, remodeling and bone fragility: how much damage is too much damage? BoneKEy reports, 4. doi:10.1038/bonekey.2015.11
13. Chapurlat R. D., Delmas P. D. (2009). Bone microdamage: a clinical perspective. Osteoporosis international, 20(8), 1299–1308.
14. Martin R. B., Burr D. B., Sharkey N. A., Fyhrie D. P. (2015). Skeletal Tissue Mechanics. New York: Springer, Second Edition.
15. Bowman S. M., Keaveny T. M., Gibson L. J., Hayes W. C., McMahon T. A. (1994). Compressive creep behavior of bovine trabecular bone. Journal of biomechanics, 27(3), 301307–305310.
16. Fondrk M., Bahniuk E., Davy D. T., Michaels C. (1988). Some viscoplastic characteristics of bovine and human cortical bone. Journal of biomechanics, 21(8), 623–630.
17. Pollintine P., Luo J., Offa-Jones B., Dolan P., Adams M. A. (2009). Bone creep can cause progressive vertebral deformity. Bone, 45(3), 466-472.
18. Deymier-Black A. C., Yuan F., Singhal A., Almer J. D., Brinson L. C., Dunand D. C. (2012). Evolution of load transfer between hydroxyapatite and collagen during creep deformation of bone. Acta biomaterialia, 8(1), 253–261.
19. Novitskaya E., Zin C., Chang N., Cory E., Chen P., D'Lima D., Sah R. L., McKittrick J. (2014). Creep of trabecular bone from the human proximal tibia. Materials Science and Engineering: C, 40, 219–227.
20. Caler W. E., Carter D. R. (1989). Bone creep-fatigue damage accumulation. Journal of Biomechanics, 22(6–7), 625–635.
21. Nilsson, M. K. (2003). Injectable calcium sulphate and calcium phosphate bone substitutes. PhD Theses, Lund University.
22. Mostakhdemin M., Amiri I. S., Syahrom A. (2015). Multi-axial Fatigue of Trabecular Bone with Respect to Normal Walking. Springer: Singapore.
23. Carter D. R., Caler W. E., Spengler D. M., Frankel V. H. (1981). Uniaxial fatigue of human cortical bone. The influence of tissue physical characteristics. Journal of Biomechanics, 14(7), 461–470.
24. Choi K., Goldstein S. A. (1992). A comparison of the fatigue behavior of human trabecular and cortical bone tissue. Journal of biomechanics, 25(12), 1371–1381.
25. O'Brien F. J., Taylor D., Lee T. C. (2003). Microcrack accumulation at different intervals during fatigue testing of compact bone. Journal of Biomechanics, 36(7), 973–980.
26. George W. T., Vashishth D. (2005). Damage mechanisms and failure modes of cortical bone under components of physiological loading. Journal of Orthopaedic Research, 23(5), 1047–1053.
27. Cotton J. R., Zioupos P., Winwood K., & Taylor M. (2003). Analysis of creep strain during tensile fatigue of cortical bone. Journal of biomechanics, 36(7), 943–949.
28. Moore T. L. A., O'Brien F. J., Gibson L. J. (2004). Creep does not contribute to fatigue in bovine trabecular bone. Transaction of ASME. Journal of Biomechanical Engineering, 126, 321-329.
29. Dendorfer S., Maier H. J., Hammer J. (2009). Fatigue damage in cancellous bone: an experimental approach from continuum to micro scale. Journal of the mechanical behavior of biomedical materials, 2(1), 113–119.
30. Haddock S. M., Yeh O. C., Mummaneni P. V., Rosenberg W. S., Keaveny T. M. (2004). Similarity in the fatigue behavior of trabecular bone across site and species. Journal of biomechanics, 37(2), 181–187.
31. Fatihhi S. J., Rabiatul A. A. R., Harun M. N., Kadir M. R. A., Kamarul T., Syahrom A. (2016). Effect of torsional loading on compressive fatigue behaviour of trabecular bone. Journal of the mechanical behavior of biomedical materials, 54, 21–32.
32. Winwood K., Zioupos P., Currey J. D., Cotton J. R., Taylor, M. (2006). Strain patterns during tensile, compressive, and shear fatigue of human cortical bone and implications for bone biomechanics. Journal of Biomedical Materials Research Part A, 79(2), 289–297.

33. Lerebours C., Buenzli P. R. (2016). Towards a cell-based mechanostat theory of bone: the need to account for osteocyte desensitisation and osteocyte replacement. Journal of Biomechanics, 49(13), 2600–2606.
34. Buganza Tepole A., Kuhl E. (2016). Computational modeling of chemo-bio-mechanical coupling: a systems-biology approach toward wound healing. Computer methods in biomechanics and biomedical engineering, 19(1), 13–30.
35. Lerebours C., Buenzli P. R., Scheiner S., Pivonka P. (2016). A multiscale mechanobiological model of bone remodelling predicts site-specific bone loss in the femur during osteoporosis and mechanical disuse. Biomechanics and modeling in mechanobiology, 15(1), 43–67.
36. Buenzli P. R. (2016). Governing equations of tissue modelling and remodelling: A unified generalised description of surface and bulk balance. Plos one, 11(4), e0152582.
37. Hambli R. (2014). Connecting mechanics and bone cell activities in the bone remodeling process: an integrated finite element modeling. Frontiers in bioengineering and biotechnology, 2(6), 1–12.37.
38. Komarova S. V., Smith R. J., Dixon S. J., Sims S. M., Wahl L. M. (2003). Mathematical model predicts a critical role for osteoclast autocrine regulation in the control of bone modelling. Bone 33, 206–215.
39. Altenbach H., Altenbach J., Zolochevsky A. (1995). Erweiterte Deformationsmodelle und Versagenskriterien der Werkstoffmechanik. Stuttgart: Deutsher Verlag für Grundstoffindustrie, 172S.
40. Zolochevsky A., Martynenko A., Kühhorn A. (2012). Structural benchmark creep and creep damage testing for finite element analysis with material tension–compression asymmetry and symmetry. Computers and Structures 100–101, 27–38.
41. Schmitt M., Allena R., Schouman T., Frasca S., Collombet J. M., Holy X., Rouch P. (2016). Diffusion model to describe osteogenesis within a porous titanium scaffold. Computer methods in biomechanics and biomedical engineering, 19(2), 171–179.

Lecture

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MANAGEMENT OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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The lecture presents modern data on acute lymphoblastic leukemia as the one of the most common malignant disease of children, youth and the elderly. The data on the major risk factors, causes, pathogenesis, clinical manifestations, as well as the main approaches to the diagnosis and treatment of this disease and possible predictions for patients in different clinical situations are described.

KEY WORDS: acute lymphoblastic leukemia, etiology, pathogenesis, clinical manifestations, diagnosis, treatment, prognosis

ВЕДЕННЯ ПАЦІЄНТІВ З ГОСТРИМ ЛІМФОБЛАСТНИМ ЛЕЙКОЗОМ

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У лекції представлені сучасні дані про гострий лімфобластний лейкоз як один з найбільш поширених злоякісних захворювань дитячого, юнацького та похилого віку. Наведено дані про основні фактори ризику, причини виникнення, патогенез, клінічні прояви, а також основні підходи до діагностики та лікування цього захворювання і можливі прогнози для пацієнтів в різних клінічних ситуаціях.

КЛЮЧОВІ СЛОВА: гострий лімфобластний лейкоз, етіологія, патогенез, клініка, діагностика, лікування, прогноз

ВЕДЕНИЕ ПАЦИЕНТОВ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ

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В лекции представлены современные данные об остром лимфобластном лейкозе как одном из самых распространённых злокачественных заболеваний детского, юношеского и пожилого возрастов. Приведены данные об основных факторах риска, причинах возникновения, патогенезе, клинических проявлениях, а также основные подходы к диагностике и лечению этого заболевания и возможные прогнозы для пациентов в разных клинических ситуациях.

КЛЮЧЕВЫЕ СЛОВА: острый лимфобластный лейкоз, этиология, патогенез, клиника, диагностика, лечение, прогноз

DEFINITION

Acute lymphoblastic leukemia (ALL) is a malignant disorder in which uncontrolled proliferation of lymphoblast occurs in the bone marrow and replaces the normal hematopoietic cells [1].

ALL is an aggressive type of leukemia and can spread to a lymph node, spleen, liver, central nervous system (CNS), and other organs. Without treatment ALL usually progresses quickly, thereby making it extremely dangerous [2].

EPIDEMIOLOGY

ALL represents 12 % of all leukemia cases, with a worldwide incidence projected to be 1–4.75 per 100000 people. Italy, United States (US), Switzerland, and Costa Rica are the countries with the highest incidence of ALL [3]. ALL has an annual incidence of up to 40 cases per million in Eastern European countries, but fewer than 20 per million in subs-Saharan Africa [4]. In Europe, ALL accounts for around 80 % of leukemia among children aged 0–14 years. Peak age of incidence occurs between the ages of 2–4 years, decreasing to become a much rarer disease of adulthood. A smaller peak occurs in people aged over 50 years.

In the year 2013, there were approximately 6020 new diagnoses of ALL in the USA resulting in 1440 death. In the year 2015, there were 6250 estimated new cases with 1450 estimated death. The number of deaths was 0.4 per 100000 men and women per year, these rates are age adjusted and based on 2008–2012 cases and deaths.

Approximately 0.1 % of men and women will be diagnosed with ALL at some point during their lifetime, based on 2010–2012 data. The prevalence of ALL in 2012 is estimated at 75176 people in the US [3–4].

The estimated overall incidence of ALL and lymphoblastic lymphoma in Europe is 1.28 per 100000 individuals annually, with significant age-related variations (0.53 at 45–54 years, ~1.0 at 55–74 years and 1.45 at 75–99 years) and that of Burkett leukemia/lymphoma is between 0.17 and 0.33 in the same age groups. These figures qualify ALL as a rare disease in adults, making assessment and care at qualified centers highly desirable. In Europe, 5-year overall survival (OS) improved from 29,8 % in the years 1997–1999 to 41,1 % in 2006–2008 ($P < 0.0001$), still as a function of age. Compared with the reference group (age 15–54 years: OS > 50 %), OS was <30% in the 55–64 years age group (hazard ratio 2.05) and <20 % in the ≥ 65 years age group (hazard ratios 2.71 and 3.75) [3–4].

RISK FACTORS

The risk factors can be divided into environmental, genetic and infectious [1, 5–7].

Environmental: ionizing radiation, paternal preconception exposure and close proximity to a nuclear facility (this implicates the link between childhood leukemia and paternal ionizing exposure in the workplace before conception or preconception); nonionizing radiation (e.g. electromagnetic fields); chemicals (hydrocarbons and pesticides); maternal alcohol, cigarette and illicit drug use.

Genetics: an identical twin is twice likely as the general population to develop ALL if his or her twin developed the illness before the age of 7 years.

Infections: a transmissible agent is potentially involved in the oncogenic process of childhood leukemia. A viral etiology has been shown for some human and animal cancers.

Other risk factors include: age, previous cancer treatment (children and adults who have had certain types of chemotherapy and radiation therapy for other kinds of cancer may have an increased risk of developing ALL), genetic disorders such as Down syndrome are associated with an increased risk.

PATHOGENESIS

Lymphoid cells are derived from pluripotent hematopoietic stem cells in the bone marrow, through stepwise maturation. ALL represents a group of B/T-precursor-stage lymphoid cell malignancies (arising from genetic insults) that blocks lymphoid differentiation and drives aberrant cell proliferation and survival.

ALL is characterized by gross numerical and structural chromosomal abnormalities including hyperdiploidy, hypodiploidy, translocations and rearrangements. However, several observations indicate that these lesions alone are insufficient to induce leukemia and cooperating lesions are required. It is suggested that the initial event confers self-renewal coupled with mutation, leading to developmental arrest and a secondary cooperative event in cell cycle regulation, tumor suppression and chromatin modification, eventually leading to establishment of the leukemic clone [8].

CLASSIFICATION

ALL can be classified as ALL B-cells or T-cells based on their stage of maturity. B-cell ALL can be divided into early pre-B, common ALL, pre-B ALL, mature B-cell ALL (also called Burkett Leukemia). T-cell ALL includes: pre-T ALL, mature T-cell ALL [1].

According to WHO, ALL is classified based on precursor lymphoid neoplasms [9]:

- B lymphoblastic leukemia/lymphoma;
- B lymphoblastic leukemia/lymphoma, NOS;

- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities;
- B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2), BCR-ABL1;
- B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged;
- B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) TEL-AML1 (ETV6-RUNX1);
- B lymphoblastic leukemia/lymphoma with hyperdiploidy;
- B lymphoblastic leukemia/lymphoma with hypodiploidy;
- B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) IL3-IGH;
- B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3) TCF3-PBX1;
- T lymphoblastic leukemia/lymphoma:

FAB classification of acute lymphoblastic leukemia includes:

- ALL-L1: Small cells with homogeneous nuclear chromatin, a regular nuclear shape, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia;
- ALL-L2: Large, heterogeneous cells with variable nuclear chromatin, an irregular nuclear shape, 1 or more nucleoli, a variable amount of cytoplasm, and variable basophilia;
- ALL-L3: Large, homogeneous cells with fine, stippled chromatin; regular nuclei; prominent nucleoli; and abundant, deeply basophilic cytoplasm. The most distinguishing feature is prominent cytoplasmic vacuolation.

SYMPTOMS

ALL usually begins abruptly and intensely, but in some cases symptoms may develop slowly. Symptoms develop when there are not enough healthy mature WBCs (leukocytes) to mount a defense against infection; there are not enough healthy blood-clotting cells (platelets) to prevent bleeding; the depleted oxygen-bearing RBCs cannot provide enough oxygen to organs [9–11].

Symptoms observed include bone and joint pain, easy bruising and bleeding (such as bleeding gums, skin bleeding, nosebleeds, abnormal periods), fatigue, fever, loss of appetite and weight loss, paleness, pain or feeling of fullness below the ribs, pinpoint red spots on the skin (petechiae), pitting edema (swelling) in the lower limbs and/or abdomen, lymphadenopathy in the neck, under arms and groin, night sweats.

DIAGNOSIS (Table)

Full blood count (FBC): anemia is usual and hemoglobin may be below 5 g/L; thrombocytopenia is also usual, to varying degrees; white blood cell count may be high, normal or low but there is usually neutropenia. Leukemia is unlikely in the presence of a normal FBC but the FBC will not always be abnormal in all cases of ALL, as some patients may not yet have marrow suppression [11]. If the blood count is abnormal, a blood film is essential to help decide whether leukocytosis is likely to be caused by malignancy or inflammation. Blood film is likely to show blast cells but can be normal if blast cells are confined to the bone marrow.

Clotting: DIC (Disseminated intravascular coagulation) may occur and this produces an elevated prothrombin time, reduced fibrinogen level and the presence of fibrin and degradation products.

Biochemistry analysis: lactic dehydrogenase levels are usually raised and rapid cell turnover may raise uric acid. Liver and renal function must be checked before initiating chemotherapy.

Bone marrow aspiration and biopsy: WHO (World Health Organization) classification requires 20 % or greater amount of blasts in bone marrow and/or peripheral blood for the diagnosis of ALL.

Immunophenotyping helps to reveal the subtypes. Positive confirmation of lymphoid rather than myeloid origin should be sought by flow cytometric demonstration of lymphoid antigens. To determine the subtype of ALL by comparing the cancer cells to normal cells in the immune system (may reveal terminal deoxynucleotidyl transferase (TdT -a specialized DNA polymerase expressed in immature, pre-B, pre-T lymphoid cells, and ALL/lymphoma cells or common acute lymphoblastic leukemia antigen (CALLA). Therapeutically, it is important to differentiate between T-cell, mature B-cell and B-cell precursor phenotypes.

Bone marrow samples should undergo cytogenetic. Hyperploid is common. A number of balanced translocations have been identified in ALL. A negative myeloperoxidase stain helps to diagnose ALL, although acute monocyte leukemia also gives negative stain with myeloperoxidase.

Testing for BCR-ABL (oncoprotein) by polymerase chain reaction or cytogenetics may help identify those patients in whom ALL arose as the lymphoblastic phase of chronic myeloid leukemia (CML).

Table 1

Diagnostic work-up in adult ALL [1]

Diagnostic step	Results/ALL subsets	Recommendations
Morphology		
Bone marrow and peripheral blood and/or cerebra-spinal fluid	Lymphoid/undifferentiated blasts (≥ 20 % bone marrow involvement); FAB L3 morphology in Burkett leukemia; CNS involvement	Mandatory Recommended Mandatory
Immunophenotype		
MPO (differential diagnosis versus AML) B-lineage markers: CD19, CD79a, cCD22 (at least 2); others: TdT, CD10, CD20, CD24, cIgM, sIg (kappa or lambda) T-lineage markers: cCD3; others: TdT, CD1a, CD2, CD5, CD7 CD4, CD8, TCR α/β or γ/δ Stem/myeloid cell markers (variable): CD34, CD13, CD33, CD117	MPO negative; B/T markers > 20 % (CD3, CD79a > 10 %) B-lineage ALL: Pro-B/B-I (CD19/CD79a/cCD22+) Common/B-II (CD10+/cIgM−) Pre-B/B-III (cIgM+/sIg−) Mature-B/B-IV (sIg+) T-lineage ALL: Pro-T/T-I (cCD3/CD7+) Pre-T/T-II (CD2/CD5) Cortical-T/T-III (CD1a+) Mature-T/T-IV (CD3+/CD1a−)	Mandatory Mandatory Mandatory
Cytogenetics/genetics		
Cytogenetics/FISH/RT-PCR CGH/SNP/GEP/NGS	ALL with adverse clinic-biological features: Ph+ ALL (rapid detection, to TKI therapy) t(4;11)+ ALL t(1;19)+ ALL other high-risk cytogenetics ALL with adverse clinic-biological features: Ph-like ALL ETP ALL NOTCH1/FBW7-unmutated/RAS/ PTEN-altered T-ALL IKZF1, CLRF2, MLL, TP53, CREBBP, RAS alterations	Mandatory Recommended for new clinical trials
MRD study		
MRD marker(s): LAIP (immunophenotype)/molecular probe (PCR)	MRD-based risk classification	Mandatory
Storage of diagnostic material		
Cell banking/storage of DNA/RNA/protein lysates	Additional/future studies	Highly recommended
HLA typing		
Patient/siblings	Early application of SCT if required	Recommended

Note: *ALL, acute lymphoblastic leukemia; CNS, central nervous system; MPO, myeloperoxidase; AML, acute myelogenous leukemia; c, cytoplasmic; IgM, immunoglobulin M; s, surface; Ig, immunoglobulin; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase polymerase chain reaction; Ph+, Philadelphia-positive; TKI, tyrosine kinase inhibitor; CGH, comparative genomic hybridization; SNP, single nucleotide polymorphism; GEP, gene expression profiling; NGS, next-generation sequencing; Ph, Philadelphia; ETP, early T-cell precursor; T-ALL, T-cell ALL; MRD, minimal residual disease; LAIP, leukemia-associated immunophenotype; PCR, polymerase chain reaction; HLA, human leucocyte antigen; SCT, stem-cell transplantation.*

DIFFERENTIAL DIAGNOSIS

Acute myeloid leukemia (AML): In many cases, the leukemic cells of AML or biphenotypic ALL are poorly differentiated with minimal amount of cytoplasm. These cells are difficult to differentiate. In such case, bone marrow biopsy, peripheral blood smear, cytochemistry, and immunological marker may be helpful in establishing the diagnosis [1].

Reactive lymphocytosis («Leukaemoid reaction»): CMV infection and Bordetella pertussis infection may present with significant lymphocytosis. It could be differentiated by bone marrow aspiration and biopsy in which will be normal hematopoiesis. Immuno-phenotyping may show increased numbers of hematogones (normal reactive B-cell progenitors).

Small-cell lung cancer: It can be differentiated by chest X-ray (pulmonary mass), and biopsy.

Merkel-cell tumor: it can be differentiated also by biopsy. The Merkel cell exhibits immunocytochemical properties of both epithelial and neuroendocrine cells.

Rhabdomyosarcoma: It can be differentiated by immunohistochemically staining (IHC) or electron microscopy may provide evidence supporting myogenic differentiation. IHC can detect muscle-specific proteins.

Aplastic anemia: It can be differentiated by absence of blast cells in peripheral blood or leucoerythroblastic features [11]. Bone marrow aspiration and peripheral blood smear are helpful in differentiating diagnosis.

Idiopathic thrombocytopenic purpura (ITP): Childhood ITP may resemble the aleukaemic pancytopenic subtype of ALL. It can be differentiated by absence of blast cells in peripheral blood or leucoerythroblastic features. Bone marrow aspiration and peripheral blood smear are also helpful in differentiating diagnosis.

TREATMENT OF NEWLY DIAGNOSED ALL

Pre-phase therapy and supportive measures [1]**.** When the diagnosis is established, treatment should start immediately, preferably in a specialized hospital; that is, physicians with experience in the treatment of acute leukemia, a well-trained nursing staff, sufficient supportive care (e.g. platelet substitution) and access to an intensive care unit. A pre-phase therapy with corticosteroids (usually prednisone 20–60 mg/day or dexamethasone 6–16 mg/day, either IV or per os) alone, or in combination with another drug (e.g. vincristine, cyclophosphamide), is often given together with allopurinol and hydration for ~5–7 days. The first intra-thecal therapy for central nervous system (CNS) prophylaxis is administered in this period in some studies. The pre-phase therapy allows a safe tumor reduction, avoiding in most cases a tumor lysis syndrome (TLS). In some cases, rasburicase may be given to prevent TLS. In cases with a very high WBC count (e.g. >100000/μl), either measure is sufficient, and a leukapheresis is needed only in very rare cases. The time needed for pre-phase therapy will also allow obtaining the results of the diagnostic work-up, e.g. cytogenetics, molecular genetics. The response to pre-phase therapy defines the chemosensitivity of the disease, and is included in some studies for risk assessment, since good responders to prednisone may have a better outcome [7, 12].

Supportive therapy should be initiated whenever necessary early on, e.g. to treat infections or to substitute platelets/erythrocytes. Severe neutropenia (< 500/μl) is often seen at diagnosis and is most frequent (>80 %) during induction therapy, causing infections and infection-related death. A joint analysis of five randomized trials revealed a shorter duration of neutropenia, and reduction in the rate of febrile neutropenia in some but not all cases, and based on that, prophylactic granulocyte colony-stimulating factor should be considered during induction therapy.

Remission induction therapy and *consolidation [9, 13–18].* The goal of induction therapy is the achievement of a CR, or even better, a molCR/good molecular response, usually evaluated within 6–16 weeks from start of chemotherapy, after which time the achievement of molCR is rather uncommon. Most regimens are centered on vincristine, corticosteroids, and anthracycline (daunorubicin, doxorubicin, rubidazone, idarubicin), with or without cyclophosphamide or cytarabine. L-Asparaginase is the only ALL-specific drug that depletes the asparagine levels and has been particularly explored in pediatric trials. It is now more intensively used in adults. Pegylated asparaginase (PEG-Asp) has the advantage of a significantly longer period of

asparagine depletion. Dexamethasone is often preferred to prednisone, since it penetrates the blood–brain barrier and also acts on resting leukemic blast cells (LBCs). There are no randomized trials comparing different induction regimens; however, there is asubstantial number of large (> 100 patients) prospective nonrandomized trials. In 6617 patients from 14 studies, the weighted mean for the CR rate was 83 % (62–92 %). Using current approaches, the CR rate had increased to 80–90 %, higher for SR patients at ≥ 90 %, and less in HR patients at ~ 75%. There is only one randomized study for induction therapy; this compares prednisone to dexamethasone, demonstrating equal outcome.

There are two chemotherapy regimens; one is a widespread schema patterned after the pediatric BFM (Berlin–Frankfurt–Munster) protocols with Induction I, Induction II, Consolidation cycles, sometimes an intermittent re-induction cycle, and is mostly used in European adult ALL trials.

Another approach is to repeat two different alternating intensive chemotherapy cycles, identical for Induction and Consolidation, accounting for a total of eight cycles, such as the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) protocol, preferentially used in the United States, but also in other parts of the world.

The rationale to use systemic high-dose (HD) therapy is particularly to reach sufficient drug levels in sanctuary sites, such as the CNS. Most protocols employ 6–8 courses which contain either HD methotrexate or HD cytarabine ± asparaginase. HD cytarabine is usually administered for 4–12 doses at 1–3 g/m^2 and methotrexate at 1–1.5 g/m^2 and up to 3 g/m^2.

Maintenance therapy [9, 13–18]. Maintenance therapy usually consists of daily 6-ercaptopurine and weekly methotrexate. In some treatment regimens, repeated cycles of vincristine, dexamethasone or other drugs in monthly or longer intervals are given. In one randomized study, the maintenance arm with reinforcement cycles was not superior to conventional maintenance therapy (37 % versus 38 % at 8 years). Treatment duration of 2,5–3 years is optimal and is usually recommended.

Omission of maintenance worsens outcome significantly in BCP-ALL, but less so in T-ALL, and not in B-ALL.

CNS prophylaxis [19]. Effective prophylaxis to prevent CNS relapse is an essential part of ALL therapy. Treatment modalities of CNS prophylaxis are CNS irradiation, intra-thecal (i.th.) methotrexate, mono- or i.th. triple (usually methotrexate, steroids, cytarabine) and systemic HD therapy with either methotrexate and/or cytarabine. With a combination of these CNS prophylactic measures, the CNS relapse rate in recent adult ALL trials could be reduced from 10 % to < 5 %. CNS irradiation is also effective to eradicate residual LBCs in the CNS; however, in most studies, it is either omitted or restricted to HR patients. Furthermore, it is given only as an irradiation of the skull (mostly 24 Gy), and no longer of the whole neuroaxis, since this aggravates cytopaenias. Patients with CNS involvement (mostly of the leptomeninges) at diagnosis are treated with the standard chemotherapy regimen, and additional i.th. applications until blast clearance in the spinal fluid. Their OS is identical to the CNS-negative cohort of patients or slightly inferior.

AGE-ADAPTED PROTOCOLS

The outcome of ALL is strictly related to the age of a patient, with cure rates from 80 % to 90 % in childhood ALL, decreasing to < 10 % in elderly/frail ALL patients. Therefore, age-adapted protocols have emerged, where the age limits are mainly directed by the hematological and non-hematological toxicities. Although there is no uniform consensus, the following age groups are separated [9–10, 13–18]:

- Adolescents and young adults (AYA), differently defined from 15 to 40 years,
- Adult ALL, age range from 40 up to 60 years,
- Elderly ALL protocols for patients above the age of 60 years, and
- Frail patients not suitable for any intensive therapy, usually considered above the age of 75 years.

Pediatric-inspired therapy provides increased drug intensity at several treatment steps, including larger cumulative doses of drugs such as corticosteroids, vincristine, L-asparaginase and consequent CNS-directed therapy, which should be strictly adhered to, with a reduced role of SCT. In a systemic review and meta-analysis in 2012, in 11 trials including 2489 AYA patients, pediatric-inspired regimens were superior to conventional adult chemotherapy. None of the trials were a

randomized comparison. In recent studies for AYAs, survival rates at 5 years were 67–78 %, compared with 34–41 % with the former protocols.

The treatment results for adult ALL patients have also improved. In the above-mentioned 14 studies, the weighted mean for DFS was 34 % (25 % at 5 years, 48 % at 3 years) and the OS 38 % (27 % at 9 years, 54 % at 5 years). Currently, the OS rates for SR adult ALL patients is 50–70 % with chemotherapy alone. The outcome for HR patients has also improved, from 20–30 % to ~50 % when they receive an allogeneic SCT in CR1. Prospective adult studies applying the same drugs and time–dose intensity, using or not using the term 'pediatric-inspired', or some using the term 'pediatric-derived', achieved identical results compared with AYAs, with survival rates of 60–70 % or more.

The incidence of ALL is increasing after the age of 50 years. Different approaches have been applied in this patient cohort. Older patients (55–91 years) with a palliative treatment had a CR rate of 43 % (34–53 %), an early death rate of 24 % (18–42 %) and an OS of only 7 months (3–10 months). In contrast, those with an intensive chemotherapy designed for adult ALL had a CR rate of 56 % (40–81 %), but still an early death rate of 23 % (6–42 %), and an OS of 14 months (3–29 months). In recent decades, several elderly specific ALL protocols have been initiated. Their principle is a less intensive therapy, based on corticosteroids, vincristine and asparaginase, and largely avoiding anthracyclines and alkylating agents, to reduce early treatment-related death. In nine prospective studies for older ALL patients (55–81 years), with this less intensive protocol, the CR rate was 71 % (43–90 %), early death decreased to 15 % (0–36 %) and OS was significant at 33 months (16–71 months). Thus, all patients, irrespective of age, should be offered a treatment.

TREATMENT OF RELAPSED OR REFRACTORY ALL

Relapsed ALL in adults is still a major clinical challenge. There is no universally accepted treatment protocol and a lack of evidence based on randomized, controlled trials [1, 6, 13, 15, 20]. However, there is consensus on the general approach to managing these patients.

Therapy-related AML should be excluded. Enumeration of CD19, CD20 and CD22 expression on blast cells is important as it may have therapeutic relevance. Cytogenetic evaluation should take into account fusion proteins that may indicate a BCR-ABL like phenotype. If allogeneic SCT is a possible therapeutic option, and if this was not done at diagnosis, the HLA profiling of the patient and siblings should be carried out urgently, and an unrelated donor search should be initiated if a sibling match is not available. In the case of Ph+ ALL, BCR-ABL1 tyrosine kinase domain mutations should be evaluated.

Overall evaluation of the clinical situation should take into account the disease-specific factors (BCP-ALL or T-ALL, BCRABL1 status), patient factors (age, performance status, organ function and presence of extramedullary disease, in particular CNS), previous therapy (with particular reference to prior allograft, anthracycline dose) and specific toxicities of prior treatment which might guide therapeutic selection (e.g. osteonecrosis, vinca alkaloid neuropathy and specific infectious complications such as fungal infections).

Treatment with a curative aim involves achievement of CR followed by allogeneic SCT. In four large trials, the outcome was very similar. The rate of second CR achieved was 44–45 %, the median OS 4,5–8,4 months (24 % at 3 years in one study). Long duration of first CR (> 2 years), then re-induction with a standard induction regimen - such as that used for original treatment - may be used. Short first CR or primary refractory disease is a very high-risk situation, and consideration should immediately be given to the availability of trials of novel agents that may be non-cross-resistant with chemotherapy. For BCP-ALL, such agents are now more widely available. Both blinatumomab and inotuzumab have shown promising results in phase II studies and are being evaluated in randomized, controlled trials where the comparator arm is 'standard of care' chemotherapy. A clinical trial involving immunotherapy with CD19 CAR T-cell therapy is also a possibility.

The most commonly used regimens in Europe are fludarabine- and anthracycline-containing regimens, for example, FLAG-Ida (fludarabine, high-dose ara-C, granulocyte colony-stimulating factor and idarubicin). Despite its common use and inclusion as 'standard of care' arm in current randomized,

controlled trials of relapsed ALL, there is remarkably little published on FLAG-Ida in relapsed ALL. Clofarabinebased regimens including cytarabine, cyclophosphamide or etoposide are also commonly used based mostly on data in childhood ALL. Liposomal vincristine is licensed for the treatment of relapsed ALL. These standard chemotherapy approaches are applicable in BCP-ALL as well as in T-ALL.

Additionally, nelarabine is licensed for this indication, and a response rate of about 50 % is noted. Myelotoxicity is mild to moderate, but the neurotoxicity can be severe and irreversible. Co-administration with agents used to treat CNS disease can increase the risk.

Patients with relapsed Ph+ ALL should be offered the new generations of TKIs, according to the results of mutational analysis of their BCR-ABL1 transcripts. Patients who have lost response to imatinib may respond to nilotinib or dasatinib and there is even an option, ponatinib, for patients with the T315I mutation. Although TKIs are not without adverse events (ponatinib, in particular, carries a risk of cardiovascular events), they are nonetheless a vastly superior option compared with repetitive treatment with myelosuppressive chemotherapy, as they preserve performance status and are better tolerated by elderly

There is no evidence of long-term survival induced by TKIs post-relapse and the majority of patients will have to receive allogeneic SCT. Second allografts are being reported, and there are case reports of good outcomes, although of uncertain long-term benefit.

Even in a palliative setting BCR-ABL1, kinase domain mutational analysis should be carried out and used to guide therapy with TKIs and to monitor treatment response and impending relapse.

COMPLICATIONS

Patients with ALL are usually immuno-compromised. There are 2 reasons for this: the lack of healthy WBCs and many of the medicines used to treat ALL can weaken the immune system.

Other commonly observed complications include pancytopenia, febrile neutropenia, tumor lysis syndrome, chemotherapy related GI toxicity, treatment-related alopecia, leukostasis, ocular involvement, chemotherapy-related CNS toxicity, avascular necrosis, anthracycline-related cardiotoxicity, vincristine-related neuropathy, bleeding (intracranial, pulmonary, GI hemorrhage), infertility [2, 6–7, 12, 19].

PROGNOSIS

Acute lymphoblastic leukemia is a curable disease, and the chance of cure for a specific patient depends on a number of prognostic factors (females tend to fare better than males; Caucasians are more likely to develop acute leukemia than African-Americans, Asians, or Hispanics; children 1–10 years of age are most likely to develop ALL and to be cured of it; cases in older patients are more likely to result from chromosomal abnormalities, etc.

Outcome is heavily age dependent in adult ALL. For the age groups under 30 years, 30–60 years, and over 60 years, complete remission rates are 90 %, 81 % and 52 % and overall survival at 3 years is 58 %, 38 %, and 12 % respectively [2, 6].

The 5-year survival rate has improved from zero six decades ago, to 85 % currently, largely because of clinical trials on new chemotherapeutic agents and improvements in SCT technology.

An individual's risk depends on a variety of clinical and biological factors. Negative prognostic features include older age, elevated WBC at presentation above 100×10^9/L, failure to achieve complete remission within 4 weeks of treatment, adverse cytogenetic and immunophenotype abnormalities. Younger patients with WBC less than 30×10^9/L and who respond to treatment within 4 weeks have the best prognosis [7].

FOLLOW-UP AND LONG-TERM IMPLICATIONS

The follow-up of asymptomatic patients should include blood cell counts and routine chemistry during maintenance therapy; usually every 2 weeks during the first 2 years to adjust treatment accordingly. Thereafter, follow-up should be 3-monthly in years 1, 2 and 3, since the majority of relapses occur within the first 2,5 years after initiation of treatment; then half-yearly in the 4^{th} and 5^{th} year. For evaluation of MRD, which is now the most important prognostic parameter, bone marrow aspiration is required 3-monthly. It is also desirable in Ph+ MRD to search for MRD (BCR-ABL) and, if possible, for mutations to switch to another TKI inhibitor.

In adults, adverse long-term effects are fewer compared with children with ALL, and most adult ALL patients are in good clinical conditions. Relevant late toxicities are: endocrinological disorders (thyroid, gonadal), osteonecrosis/osteoporosis, skin and mucosal disorders, cataract, cardiovascular disorders, infection, graft versus host disease/sicca syndrome, fatigue and cognitive disorders. Second malignancies can also occur but with a low frequency (< 3 %) after chemotherapy as well as SCT. Long-term observation including quality-of-life assessment of cured ALL patients is an essential part of treatment optimization studies [1].

CONCLUSIONS [1]

Diagnostic work-up of ALL:

- Morphology, immunophenotype and cytogenetics to confirm the diagnosis and ALL subsets are mandatory.
- New genetics and molecular genetics are recommended to detect rare subtypes, such as Ph-like ALL, ETP ALL.
- Targets for therapy with TKIs or antibodies have to be identified.
- Minimal residual disease by immunophenotype or molecular probe at diagnosis, for MRD-based risk classification and treatment algorithm, mandatory.

Risk assessment and prognostic factors:

- It is essential to stratify patients as standard-risk or high-risk patients.
- Risk stratification is currently determined by a combination of prognostic factors at diagnosis and treatment-related parameters, preferentially MRD.
- MRD during therapy is now the most relevant prognostic parameter for treatment decisions.

Treatment:

- Chemotherapy includes induction therapy 1–2 months, consolidation cycles (alternating) 6–8 months and maintenance therapy 2–2,5 years.
- Ongoing chemotherapy protocols for AYAs use pediatric-type regimens.
- Prophylactic treatment to prevent CNS relapse is mandatory.
- Anti-CD20 rituximab in combination with chemotherapy is strongly recommended for Burkett leukemia/lymphoma.
- Anti-CD22 immunoconjugates directed against CD22 currently under investigation.
- Anti-CD19; activation of patients' own T cells directed against CD19.
- Bispecific (CD3/CD19) blinatumomab under investigation.
- Chimaeric antigen receptor-modified T cells directed against CD19 in early phase.
- A TKI should be combined with chemotherapy in front-line therapy.
- The TKI imatinib (400–800 mg/day) should be administered continuously, also post-SCT.
- Prolonged monitoring of BCR-ABL-1 MRD is recommended, as well as resistance mutation screening. In case of persisting MRD, increasing MRD level, or resistance mutation, switch to a second- or third-generation TKI.
- AlloSCT in CR1 significantly improves OS and EFS in high-risk patients/MRD+ patients and is the best post-remission option for Ph+ ALL and MLL-rearranged ALL.
- Conditioning regimens are age-adapted with full allo versus RIC for elderly patients or patients unfit for full conditioning.
- The role of autoSCT should be investigated for MRD-negative patients, in the setting of clinical trials.
- All patients in CR ≥ 2 are candidates for alloSCT.

Approach for relapsed/ refractory ALL:

- Full diagnostic work-up necessary to exclude/reveal clonal aberrations, and to provide bases for targeted therapies.
- Different treatment for patients with short versus long first remission duration (> 18/24 months) where re-induction is considered.
- Treatment; there is no standard re-induction therapy established, most often used new drugs.

REFERENCES

1. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up / [D. Hoelzer, R. Bassan, H. Dombret, et al] // Ann Oncol. – 2016. – № 27 (suppl_5). – v. 69–v.82.

2. BCR-ABL translocation as a favorable prognostic factor in elderly acute lymphoblastic leukemia patients in potent tyrosine kinase era / [J. M. Byun, Y. Koh, D. Y. Shin, et al.] // Haematologica. – 2017. – № Jan 12.
3. The Danish National Acute Leukemia Registry / [L. S. Ostgard, J. M. Norgaard, K. K. Raaschou-Jensen, et al.] // Clin Epidemiol. – 2016. – № 8. – p. 553–560.
4. Evolving prevalence of haematological malignancies in orphan designation procedures in the European Union / [B. Polsinelli, S. Tsigkos, F. Naumann-Winter, et al.] // Orphanet J Rare Dis. – 2017. – № 12 (1). – p. 17.
5. Infection as a cause of childhood leukemia-virus detection employing whole genome sequencing / [C. Bartenhagen, U. Fischer, K. Korn, et al] // Haematologica. – 2017. – Feb 2.
6. The Relationship Between Risk Factors and Survival in Adult Acute Lymphoblastic Leukemia / [A. Allahyari, S.M. Hashemi, F. Nazemian, et al] // Iran J Cancer Prev. – 2016. – № 9 (4). – p. 5045.
7. Analysis of outcomes and prognostic factors of acute lymphoblastic leukemia patients treated by MCP841 protocol: A regional cancer center experience / [A. Kapoor, A. Kalwar, N. Kumar, et al] // J Res Med Sci. – 2016. – Mar 15. – № 21. – p. 15.
8. Minimal residual disease detection in Tunisian B-acute lymphoblastic leukemia based on immunoglobulin gene rearrangements / [S. Besbes, W.S. Hamadou, M.L. Boulland, et al] // Braz J Med Biol Res. – 2017. – № 50 (1). – e 5426.
9. Aldoss I.T. Treatment of Acute Lymphoblastic Leukemia in Adults: Applying Lessons Learned in Children / I.T. Aldoss, G. Marcucci, V. Pullarkat // Oncology (Williston Park). – 2016. – Dec 15. – № 30 (12).
10. Long-term destiny of adolescents and young adults with de novo acute lymphoblastic leukemia treated with a pediatric protocol type / [M. A. López-Hernández, M. Alvarado-Ibarra, J. L. Álvarez-Veral, et al] // Gac Med Mex. – 2016. – № 152 (5). – p. 439–443.
11. Bogun L. V. Anemia of chronic disease / L. V. Bogun // The Journal of V. N. Karazin Kharkiv National University, series Medicine. – 2015. – № 29. – p. 81–87.
12. Impact of Aberrant Antigens in the Outcome of Patients with Acute Leukemia at a Referral Institution in Mexico City / [S. Rodríguez-Rodríguez, A. Pomerantz, R. Demichelis-Gómez, et al] // Rev Invest Clin. – 2016. – № 68 (6). – p. 305–313.
13. Adult Acute Lymphoblastic Leukemia Treatment (PDQ®): Health Professional Version [Electronic source] / Access: https://www.ncbi.nlm.nih.gov/pubmed/26389171.
14. Wang L. Tyrosine Kinase Inhibitor for Treatment of Adult Allogeneic Hematopoietic Stem Cell Transplantation Candidate with Philadelphia-Positive Acute Lymphoblastic Leukemia / L. Wang, D. H. Liu // Chin Med J. – 2017. – № 30 (2). – p. 127–129.
15. Mixed-phenotype acute leukemia: suboptimal treatment when the 2008/2016 WHO classification is used / [A. Pomerantz, S. Rodriguez-Rodriguez, R. Demichelis-Gomez, et al] // Blood Res. – 2016. – № 51 (4). – p. 233–241.
16. Clonal evolution in therapy-related neoplasms / [E. Fabiani, G. Falconi, L. Fianchi, et al] // Oncotarget. – 2017. – № Jan 5.
17. Use of PEG-asparaginase in newly diagnosed adults with standard-risk acute lymphoblastic leukemia compared with E. coli-asparaginase: a retrospective single-center study / [W.J. Liu, H. Wang, W.D. Wang, et al] // Sci Rep. – 2016. - Dec 21. – № 6. – p. 39463.
18. A childhood chemotherapy protocol improves overall survival among adults with T-lymphoblastic lymphoma / [M. Y. Zhu, H. Wang, C. Y. Huang, et al] // Oncotarget. – 2016. – № 7 (25). – p. 38884-38891.
19. The central nervous system microenvironment influences the leukemia transcriptome and enhances leukemia chemo-resistance / [J. S. Gaynes, L. M. Jonart, E. A. Zamora, et al] // Haematologica. – 2016. – Dec 29.
20. Characterization of Rare, Dormant, and Therapy-Resistant Cells in Acute Lymphoblastic Leukemia / [S. Ebinger, E. Z. Özdemir, C. Ziegenhain, et al] // Cancer Cell. – 2016. – Dec 12. – № 30 (6). – p. 849–862.

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