Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

АВГУСТ 2019 (№ 4(48))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
Общество с ограниченной ответственностью «Синапс»
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Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»
ООО «Сам Полиграфист»
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru

Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Почта России» 87732

DOI: 10.20514/2226-6704-2019-4

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

AUGUST 2019 (№ 4(48))

FOUNDER AND PUBLISHER
«SYNAPSE» LLC
107076, Moscow, Korolenko str., 3A, of. 18B
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PAGE-PROOFS
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ADVERTISING
Aymaletdinova Adelya
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Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»
«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Russian Post» 87732

DOI: 10.20514/2226-6704-2019-4

СОДЕРЖАНИЕ

Лекции

Обзорные статьи

Оригинальные статьи

Разбор клинических случаев

С 2016 ГОДА СТАТЬИ В ЖУРНАЛ ПРИНИМАЮТСЯ ЧЕРЕЗ РЕДАКЦИОННУЮ ПЛАТФОРМУ:
http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

НОВЫЕ ПРАВИЛА ПУБЛИКАЦИИ АВТОРСКИХ МАТЕРИАЛОВ (2019):
http://www.medarhive.ru/jour/about/submissions#authorGuidelines

CONTENT

SINCE 2016, ARTICLES IN THE JOURNAL HAVE BEEN ACCEPTED THROUGH THE EDITORIAL PLATFORM:

http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

NEW GUIDELINES OF PUBLICATION FOR AUTHORS OF ARTICLES (2019):

http://www.medarhive.ru/jour/about/submissions#authorGuidelines

DOI: 10.20514/2226-6704-2019-9-4-245-252 UDC 616-053.9-07

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ABOUT THE BASICS OF COMPREHENSIVE GERIATRIC ASSESSMENT

Abstract

The article covers the principles of comprehensive geriatric assessment — an interdisciplinary diagnostic procedure aimed at developing a plan of treatment, long-term monitoring and support of an elderly person. The components of a comprehensive geriatric assessment, including the determination of physical, functional, psychological and social status of the subject, are reflected. During the process of analyzing the patient's physical status, the age-related features of the functioning of various organs and systems, knowledge of which is necessary for the development of a targeted geriatric care strategy, should be taken into account. Involution of the respiratory organs is characterized by a decrease in the respiratory surface, atrophic processes in the mucous and lymphoid tissues, and an increased risk of developing bronchoobstructive syndrome. Degenerative-sclerotic changes in the cardiovascular system contribute to the development of circulatory failure, sinus node dysfunction, increased sensitivity to stress factors, orthostatic hypotension, etc. With age, the secretory function of the gastrointestinal tract decreases, and the functional ability of the liver is limited. Reducing the reserve capacity of the kidneys provokes the development of inflammatory processes and contributes to the dehydration of the body. In older people, the risk of developing diabetes, hypothyroidism and hyperparathyroidism increases. The growth of connective tissue in the blood-forming organs limits the functionality of the blood system. Age-related changes in the musculoskeletal system are characterized by a decrease in muscle mass and the development of osteoporosis. Drug therapy is also being analyzed, since polypharmacy in the elderly is associated with a particularly high risk of developing side effects of the drugs. Assessment of the functional status implies the determination of the self-service ability and the degree of a person's independence from the help of others by his/her ability to perform basic functions, activities in everyday life and instrumental activity. The psycho-emotional status is judged by the emotional background of the patient and his/her cognitive functions. Social and household status is estimated by the living conditions of an elderly person. Based on the results of a comprehensive geriatric assessment, an individual management plan is drawn up, the implementation of which is possible with the combined efforts of the geriatrician and a team of medical specialists, relatives, and social workers.

Key words: *geriatrics, comprehensive geriatric assessment, senile asthenia*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 05.05.2019
Accepted for publication on 03.07.2019

For citation: Farkhutdinova L. M. ABOUT THE BASICS OF COMPREHENSIVE GERIATRIC ASSESSMENT. The Russian Archives of Internal Medicine. 2019; 9(4): 245-252. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-245-252

FRAX — Fracture Risk Assessment Tool, BP — blood pressure, CGA — comprehensive geriatric assessment

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Old age needs so little
but needs that little so much.

Margaret Willour

Relevance

Around the world, one of the central health and social problems is the preservation of the health and quality of life of senior citizens. Physiological aging and geriatric attention are aimed at an adverse variant of this process which is senile asthenia. In Russia, this syndrome is observed in 84 % of people of elderly and senile age, while in Germany this figure is 66.4 %, Finland — 60 %, USA — 55 %, Switzerland — 50 %, Belgium — 40 %. Reduction of physical and functional activity in senile asthenia leads to the development of dependence on physical assistance in everyday life and deterioration of health prognosis. Diagnosis of senile asthenia syndrome is based on a comprehensive geriatric assessment (CGA), which, in turn, is the basis for the organization of medical care for elderly people [1, 2, 7, 9, 13, 15].

Background

For many years, it was believed that diseases in elderly people have, in the vast majority of cases, a poor prognosis. In 1943, the British physician Marjorie Warren published an article which for the first time confirmed the potential reversibility of health problems in elderly patients. According to the author, the specific needs of this group of patients, unlike young people, justify the need for a special approach in providing them with medical care, which should be carried out by a team consisting of doctors of different profiles, nurses and social workers. Marjorie Warren also proposed to divide the elderly into groups taking into account their degree of dependence on others. This approach formed the basis for a comprehensive assessment of the health of elderly patients, which was gradually improved.

In 1963, WHO proposed to divide elderly people into socially active, individually active and dependent on others, i.e. along with the physical condition to assess the ability of a person to maintain activity in everyday life. The analysis of comprehensive geriatric assessment efficacy conducted in 1993 showed that this approach can reduce mortality by 18 % and the risk of re-hospitalization — by 12 %, increase cognitive function by 41 %, and return 25 % of patients to independent living [7, 10].

Definition

Comprehensive geriatric assessment is a method of examination that includes determination of physical, functional, psycho-emotional and social status of an elderly person with the subsequent development of an action plan to improve the quality of life.

Components of a comprehensive geriatric assessment

1. Physical status

The analysis of the health status of an elderly person is based on the knowledge of age-related changes in organs and systems, which are more or less characterized by the development of dystrophic, sclerotic processes and a decrease in the reserve capacity of the body. Significant senile involution can reduce the quality of life. However, understanding the pathogenesis of body functioning in elderly patient allows to give a correct assessment of the results of his/her examination and to develop a targeted strategy of geriatric care.

The *respiratory system* with age is characterized by the development of chest deformation due to degenerative changes in the vertebral bodies and intervertebral discs, as well as by decrease in the elasticity of the lung parenchyma, which can lead to the formation of senile emphysema and a decrease in the respiratory surface by 40–45 %, contributing to dyspnea even with low physical activity. Atrophic changes in the tracheal and bronchial mucosa along with involution in lymphoid tissue significantly increase the risk of inflammatory respiratory diseases and contribute to their torpid course. The number and sensitivity

of β2-adrenergic receptors in the bronchi decrease with age, while the density of cholinergic receptors remains unchanged, and the obstructive syndrome can be the consequence not only of chronic obstructive pulmonary disease, but also cardiovascular diseases, cancer, side effect of pharmacotherapy, the impact of environmental factors, etc. Fibrosis of capillaries with an increase in brittleness provokes hemoptysis when straining and heavy coughing.

Morphofunctional state of the *cardiovascular system* is also characterized by sclerotic changes with an increase in the number of collagen fibers, a decrease in the number of elastic fibers and muscle atrophy. As a result of these processes, the vascular wall becomes rigid, blood flow and pulse wave velocity, and peripheral resistance increase, which causes senile systolic hypertension. Degenerative and sclerotic changes in the myocardium lead to a decrease in shock ejection, impaired diastolic relaxation, contributing to the development of heart failure. In the endocardium, the formation of valve calcification is possible, which is most often manifested by aortic stenosis or mitral valve prolapse. Because of fibrous degeneration in the cardiac conductive system, the number of cells generating and conducting impulses decreases (by the age of 80 years 10 % of pacemaker cells remain in the sinoatrial node from their number at a young age), which causes dysfunction of the sinus node, a tendency to bradycardia, atrial fibrillation, ventricular premature beats, various forms of blockade. With the development of sick sinus syndrome, episodes of tachy- and bradycardia are observed, which cause sudden dizziness, syncopal state and loss of consciousness.

It should be borne in mind that the elderly heart is characterized by a higher sensitivity to psycho-emotional stress, as well as to effects of factors such as alcohol, smoking, infection, intoxication, drugs, etc.

Elderly people are characterized by instability of blood pressure (BP) with fluctuations from high to low values up to orthostatic collapse, which is associated with a weakening of neurohumoral regulatory mechanisms. In this regard, the use of antihypertensive drugs, neuroleptics, benzodiazepines, antiparkinsonian agents may be accompanied by the development of orthostatic hypotension. The detection of low BP is of great clinical importance. The reduction of BP increases the risk of Alzheimer's disease, and the reduction of diastolic BP to 60 mm Hg or lower exacerbates myocardial ischemia and reduces life expectancy. It is shown that ideally selected for geriatric patient hypotensive therapy in hospital conditions after discharge from the hospital can cause severe hypotension up to cardiovascular disaster, due to the expansion of physical activity. It should be borne in mind that in elderly people, the relationship of hypertension with increased mortality has been proven for "strong" patients, while "fragile" patients have no such relationship. The impact on the quality of life of life-long therapy with antihypertensive drugs has not been studied. According to study results, BP in long-living persons is directly correlated with cognitive functions, and the decrease in BP to less than 130 mm Hg does not reduce the risk of cardiovascular disease. In this regard, the recommended figures of BP in persons under 80 years are not more than 140 mm Hg, at the age over 80 years — up to 150 mm Hg in "strong" patients and up to 180 mm Hg — in "fragile" patients [3, 6, 7].

Involution of the *digestive system* is characterized by atrophic changes throughout the gastrointestinal tract. Reducing the filamentous papillae of the tongue violates the perception of taste and reduces appetite. Decrease in secretory activity of the salivary glands along with the loss of teeth causes difficulty in the mechanical processing of food and digestive disorders in the oral cavity. There is also a decrease in secretory function of the stomach, pancreas (the mass of pancreatic tissue with age is reduced by 1.5–2 times), and violation of parietal digestion and absorption processes. All these changes contribute to weight loss with aging. An unfavorable aspect is a decrease in body weight by 6.5 % for 6 months or 5 % for 1 month. A body mass index of less than 20 kg/m^2 increases the risk of osteoporosis, while a value of 30 kg/m^2 is associated with the lowest mortality.

With age, the weight of the liver decreases, which is most pronounced in persons older than 80 years. Limitation of liver function (synthetic function, detoxification) is manifested in psycho-emotional stress, eating disorders, diet violation, the influence of adverse environmental factors, poisoning, the use of a number of drugs.

The *urinary system* is characterized by renal tissue sclerosis, which leads to the loss of 1/3–1/2 of the nephrons with age, which causes a limitation of the reserve capacity of the kidneys under stress, for example, the phenomenon of renal failure can be observed in unilateral pyelonephritis. Pyelonephritis is the main nephrological problem in geriatrics, which is facilitated by age-related disorders of the urodynamics and blood supply to the kidneys, as well as deterioration of immunity. The prevalence of pyelonephritis in the elderly increases by 4–5 times. However, the clinical symptoms of the disease are often subclinical. There are no such local manifestations as dysuria, lower back pain, and intoxication syndrome prevails — weakness, adynamia, lack of appetite, sleep disturbance, confusion, etc. Most cases of bacterial shock in acute attack of pyelonephritis are observed in elderly people.

Sclerosis of the bladder wall reduces its capacity, which causes increased frequency of urination.

The weakening of the sphincter function leads to urinary incontinence, and, indirectly, can cause the fall of an elderly person with a hasty rise, especially at night.

Patients suffering from urinary incontinence often try to limit fluid intake, which leads to dehydration, aggravating orthostatic hypotension. The risk of dehydration increases with age also due to a decrease in the feeling of thirst and appetite, a decrease in the activity of the antidiuretic hormone and the sensitivity of the kidneys to it. Severe dehydration increases the risk of falls and mortality in elderly patients. Diagnosis of this disorder at the initial stages is based on the detection of dry tongue, reduced skin turgor, orthostatic BP reduction and weight loss.

One of the main changes in *endocrine organs* is a decrease in the endocrine function of the pancreas. In this regard, age is considered as a diabetes-inducing factor (the second most important after obesity). The incidence of diabetes mellitus in persons over 60 years is 10 %, older than 80 years — 20 %, while in the population — up to 5 %.

However, the elderly age is characterized by a violation of adaptation mechanisms against hypoglycemia. For this reason, a decrease in blood sugar, which is a stress for the body, accompanied by the release of catecholamines, increases the risk of cardiovascular events — rhythm disturbances, myocardial infarction, stroke, retinal hemorrhage, etc., up to fatal. Detection of hypoglycemia is an important task in the supervision of elderly patients, and it should take into account the typical subclinical nature of adrenergic signs, such as excitement, sweating, hunger, etc., and the prevalence of neuroglycopenic symptoms — asthenia, headache, disorientation, behavioral disorders.

The decrease in blood sugar in older people not suffering from diabetes is usually associated with violations of the diet.

With age, the prevalence of hypothyroidism increases, and it occurs in 10–15 % of women older than 60 years. In this case, the clinical pattern of the disease is largely similar to age-related changes — memory loss, slowness, dry skin, etc. This disease is diagnosed by the level of thyroid-stimulating hormone, the determination of which is provided in the process of CGA.

Among endocrine pathology, parathyroid adenoma — primary hyperparathyroidism — is the third most common after thyroid diseases and diabetes (1–2 cases per 1,000 people). The peak incidence falls at the age of 60. Clinical manifestations are due to the violation of calcium and phosphorus metabolism — osteoporosis, urolithiasis, etc. One of the main laboratory signs of the disease is increased blood calcium, the determination of which is included in CGA [7, 11, 12, 17].

In *hematopoietic organs*, connective tissue grows with age, as a result, the volume of hematopoietic tissue in persons older than 70–75 years can be about 30 % of its volume in young people. Clinically, these changes are manifested in stressful situations — with intoxication, infection, psycho-emotional and physical activity, etc. Due to the limited functionality of the blood system in the elderly, leukocytosis with a shift to the left is rare, inflammatory processes are more torpid in nature. Restoration of blood cell composition after blood loss occurs twice as slow. Chronic blood loss from the gastrointestinal tract is the most common cause of iron deficiency anemia in the elderly. Atrophic processes in the gastric mucosa are accompanied by the development of B12-deficiency anemia. Tissue hypoxia also contributes to the appearance of age-related "stiffness" of red blood cells, which complicates microcirculation and tissue metabolism.

The weakened reaction of lymphocytes against mutagens provokes cancer.

With age, there are significant changes in the protein spectrum of blood plasma — there is a shift towards coarse proteins, which is associated with an increase of up to 40 % in the erythrocyte sedimentation rate after 60 years.

Age-related changes in the *musculoskeletal system* are characterized by the involution and atrophic processes in the muscles, articular apparatus, cartilage and bone tissue. Degenerative changes in skeletal muscle, or sarcopenia syndrome, leads to a gradual loss of muscle mass, the reduction of which after 50 years is 10 % every decade, with the most pronounced atrophy in the muscles straightening the trunk. Sarcopenia is accompanied by a decrease in muscle strength and walking speed, and causes a fear of fall. Degenerative and dystrophic changes in the connective tissue structures of the joint provoke ruptures of tendons and ligaments (the most frequent are ruptures of tendons of the shoulder muscles, the long head of the biceps, the posterior tibial tendon, the patellar ligament and the heel tendon). Degenerative changes in cartilage are accompanied by calcification and even ossification with the development of osteoarthritis, most often affecting the interphalangeal, knee, hip, shoulder joints and spinal joints. The main consequence of the involution and atrophy in bone tissue is osteoporosis.

After 60 years, one of the main reasons for the development of osteoporosis is a negative calcium balance, due to a decrease in the use of dairy products and a violation of their absorption as a result of a decrease in the formation of hydrochloric acid, atherosclerosis of intestinal vessels, as well as a deficiency of vitamin D, mostly formed in the skin under sunlight exposure. The lack of calcium stimulates the production of parathyroid hormone, which facilitates calcium release into the blood from bone tissue, which is accompanied by bone destruction.

Clinical symptoms of osteoporosis are a decrease in height by 4 cm or more compared to the age of 25 years or 2 cm per 1–3 years, the distance between the back of the head and the wall of 5 cm or more, and between the lower ribs and the ilium of less than 2 cm, and swelling of the abdomen. Instrumental methods for diagnosis of osteoporosis are densitometry, skeletal radiography, revealing osteoporotic fractures. For densitometry, the "gold standard" is dual-energy X-ray absorptiometry. If during the evaluation of complaints, history, physical examination and spinal radiography low traumatic fractures are not detected, the decision on therapy for osteoporosis is made on the basis of a 10-year probability of developing low traumatic fracture, which is determined according to FRAX scale (Fracture Risk Assessment Tool). The FRAX evaluation is highly recommended to people who are not able to undergo densitometry (unavailability of equipment) and in cases when densitometry revealed osteopenia. It should be emphasized that the presence of low-traumatic fractures in the history, especially multiple, is an indication for therapy regardless of densitometry and FRAX score.

The condition of the patient's *vision* is assessed by the ability to read text, drug names, and to recognize people. Capacity for *hearing* is judged by whether the subject asks again or not. It should be borne in mind that older people hear lower frequencies better.

When conducting CGA the ongoing drug therapy is also analyzed. It is important to note that polypragmasy in the elderly is associated with a higher risk of side effects due to the increased sensitivity of the body to drugs, so their number should be as limited as possible. Preference is given to drugs aimed at the treatment of the most prognostically significant diseases — coronary heart disease, hypertension, atrial fibrillation, heart failure, diabetes. In addition, elderly people are not recommended to receive generic drugs*, because their use is characterized by a higher frequency of side effects compared with original drugs.

Special attention is required for drugs, the use of which involves dose control (hypotensive, hypoglycemic), as well as drugs that are often abused by the elderly (sedatives, Corvalol, etc.).

In the process of CGA, bad habits are also clarified, especially since sensitivity to their adverse effects increases with age, the facts of harmful environmental effects, as well as working conditions in the history [3–5, 8].

* Generics may differ from the original drugs by the composition of excipients.

2. Functional status

The possibility of self-service and the degree of independence on the help of others by person's ability to perform basic functions, activities in everyday life and instrumental activity are determined.

Daily activity of the subject characterizes their ability to independently eat, dress, go to the toilet, wash, move around the room, etc.

To assess ability to perform basic functions, patient is asked to:

- put his/her hands behind the head, behind the back at waist level (ability to comb, dress, perform hygienic procedures);
- touch his/her thumb on the opposite leg when seated (ability to wear shoes, cut toenails);
- squeeze the fingers of the doctor with both hands (the ability to open doors, cans);
- hold a piece of paper between thumb and index finger (ability to select and hold objects);
- rise from a chair without the help of hands (ability of free movement).

If the subject can perform the task, 2 points are assigned, if he/she cannot — 0 points and 1 point if the task is performed with difficulty.

To test activities of daily living, the Barthel index is used, which is given in the CGA report. This scale determines the ability to eat, wash, dress, control pelvic functions, take a bath, go to the toilet, get out of bed, move, climb the stairs. Performance of each function is rated in points, the greatest number (up to 20 points) is given when the function is performed independently, 0 points — in case of full dependence on others, 5–10 points — if partial help is required. The total score from 0 to 20 means full dependence, 21–60 — severe dependence, 61–90 — moderate dependence, 91–99 — mild dependence and 100 — no dependence.

Instrumental activity of an elderly person reflects his/her ability to live independently and solve everyday problems. The CGA report contains the scale for daily instrumental activity — IADL (Instrumental Activities of Daily Living by W. B. Abrams, M. H. Beers, R. Berkow et al., 1995). It analyzes the ability to use the phone, to get to places outside the usual walking distances, to go to the grocery store, to cook, to do household chores, to take medication, to manage money. Each item is evaluated according to a 3-point system: execution — 3 points, execution with help — 2 points, failure to execute — 1 point. A total of less than 27 points indicates a decrease in instrumental activity.

Depending on the results, the need for external care, partial or permanent, at home or in a specialized geriatric institution is considered. However, the "independent" category permits the use of auxiliary aids.

3. Mental status

Preservation of the higher nervous activity of the patient is determined by his/her emotional background and cognitive functions. For this purpose, a special scale for the diagnosis of depression and dementia is used.

For identification of mood disorders there are many questionnaires, of which the most used was the scale of depression GDS-15 (Geriatric Depression Scale), including the following 15 questions:

1. Are you basically satisfied with your life?
2. Have you dropped many of your activities and interests?
3. Do you feel that your life is empty?
4. Do you often get bored?
5. Are you in good spirits most of the time?
6. Are you afraid something bad will happen to you?
7. Do you feel happy most of the time?
8. Do you feel helpless?
9. Do you prefer to stay home rather than going out and doing something new?
10. Do you feel you have more problems with memory than most people?
11. Do you think it is wonderful to be alive?
12. Do you feel pretty worthless the way you are now?
13. Do you feel full of energy and vitality?
14. Do you feel that your situation is hopeless?
15. Do you think that most people are better off than you are?

One point is credited for answering "Yes" for questions 2, 3, 4, 6, 8, 9, 10, 12, 14 and 15, as well as for answering "No" for questions 1, 5, 7, 11 and 13. A total score of 5 and above indicates probable depression.

One of the most common tests for assessing mental health is drawing a clock face with the time usually asked to mark with arrows the time 14:45 or 11:10. For the diagnosis of dementia, a Mini-Cog test is often used, consisting of three stages, which

takes 3–5 minutes. At the first stage three words (e. g., lemon, key, ball) are named and offered to remember, at the second one — it is proposed to draw a clock and to mark the time, and at the third stage — to recall three words. In Alzheimer's disease, short-term memory is affected earlier, in vascular dementia — long-term memory, and so in the first case the patient can draw a clock, but will not recall the words, in the second case — will remember the words with a hint, but will not draw the clock-face.

A brief MMSE (Mini-Mental State Examination) scale was widely used for the diagnosis of dementia. It contains 9 tasks and 30 questions evaluating cognitive domains such as orientation in time, location, memory, perception, attention and speech. The maximum score according to the test is 30 points, and a score of 27 points and below is regarded as probable cognitive deficiency.

These types of testing of mental abilities have low sensitivity to detect mild cognitive disorders. For their screening, it is recommended to use a more sensitive diagnostic tool — Montreal Cognitive Assessment (MoCA) scale, specially designed to detect moderate cognitive impairment in patients with normal MMSE results. The test evaluates 8 categories of cognitive process: Executive and visual and constructive skills, naming, memory, attention, speech, abstraction, delayed memory and orientation. The maximum score is 30 points, the threshold is 26 (if general education is less than 12 years — 25). Testing with MMSE and MoCA scales takes about 10 minutes.

It is important to emphasize that the assessment of cognitive functions of an elderly person should take place in a calm, friendly environment and requires patience and tact from the doctor.

In psychological terms, an important factor is the relationship with relatives, the lack of attention from whom can be the leading cause of the depressed condition in the elderly person, which in turn exacerbates the somatic problem. It should be noted that in contrast to the physical capabilities that decrease with aging, intellectual reserves have no age limits. The most preserved is the emotional sphere, and even a patient with dementia is able to respond to the feelings shown to them.

However, a person's perception of the world depends on his/her inner world.

Social status

As the results of studies have shown, the prevalence of senile asthenia is highest among divorced people and widowers, slightly lower in persons who have never been married, and the lowest in elderly people who are married. This syndrome is more common in rural areas.

Living conditions are important for maintaining the vitality of an elderly person. They pay attention to the comfort and safety of life — lighting, air temperature, the possibility of unhampered movement, etc. In Israel, where the gerontological society has existed since 1956, the position of a social worker is provided in each hospital, and this is a specialist with higher education who knows the legal framework, informs about possible assistance to the patient, assists in the preparation of documents.

The doctor needs to get an idea of the material well-being and the circle of persons who could provide assistance, and if necessary, provide daily care, organize leisure. In Western countries, for example, there are "grandfather gardens", where geriatric patients are given classes, and a wide range of board games and educational toys are provided.

Assessment of social status implies determination of the most adequate living conditions for the patient — living alone, with family or in a nursing home. However, it should be emphasized that by the end of the 20th century sociologists had come to the conclusion that a person should grow old in the family [2, 10, 13, 14, 16, 18].

Conclusion

Comprehensive geriatric assessment is the thorough examination of an elderly person, based on the results of which the geriatric physician makes an individual plan of patient management, including recommendations on diet, physical activity, drug and non-drug therapy, household arrangement, adaptive technologies, social support and care. The geriatric physician is aimed at bringing together a team of health care professionals, relatives and social workers, the success of which is based on a friendly and delicate attitude towards the elderly patient. "Know how to be lenient to the human weaknesses of the elderly," Vasily Sukhomlinsky wrote.

The possibility of a happy longevity, of course, primarily depends on the care of loved ones, because the elderly person especially needs an atmosphere of love and mutual understanding.

However, the preservation of the quality of life in an elderly person depends largely on the possibility of self-realization at a later age, including professional skills. The expert analysis of the so-called "demographic burden" showed its artificial aggravation. In fact, the financial return for use of labor resources of the elderly population is many times higher than the costs, and the change in the age structure of the labor force has various effective solutions. In 2002, during the second United Nations Assembly on ageing, held in Madrid, the Madrid International Plan of Action to ensure that every person has a safe and dignified old age, as well as the opportunity to participate in society as a full citizen was adopted.

Geriatrics is one of the youngest and at the same time the most humane medical specialties, which not only allows to solve the problems of longevity, but also contributes to the moral revival of society.

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DOI: 10.20514/2226-6704-2019-9-4-253-259 UDC 616.98-07-08:579.852.13

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THE DIFFICULTIES OF EARLY DIAGNOSIS AND TREATMENT OF BOTULISM

Abstract

The popularity of home canning contributes to a sufficiently high incidence of botulism worldwide. The canned products containing botulinum toxin do not change neither color, taste, nor smell of contents of canned food. A distinctive feature of the paralytic syndrome in botulism is its symmetry and the absence of a violation of sensitivity. The criteria for the severity of the course of botulism are considered a violation of swallowing liquid food and symptoms of difficulty breathing. A violation of swallowing liquid food and the severity of acute respiratory failure are considered criteria of the severity of the course of botulism. The paper presents the features of the therapy of the patients with botulism in the intensive care unit. Clinical examples illustrate the difficulties in recognizing botulism at the early stage of the disease, which are due to the polymorphism of the clinical picture of botulism and the similarity of symptoms with other diseases. Most commonly, patients with botulism are diagnosed with acute intestinal infection or the neurological pathology. Patients are not hospitalized in a timely manner, which can affect the outcome of the disease. The ability to recognize botulism at the prehospital stage is necessary for all doctors.

Key words: *botulism, botulism therapy, early diagnosis of botulism, anti-botulinum serum, hyperbaric oxygenation, mechanical ventilation*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 15.04.2019 г.
Accepted for publication on 19.06.2019 г.

For citation: Nikiforov V. V., Tomilin Yu. N., Chernobrovkina T. Ya. et al. THE DIFFICULTIES OF EARLY DIAGNOSIS AND TREATMENT OF BOTULISM. The Russian Archives of Internal Medicine. 2019; 9(4): 253-259. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-253-259

HBO — hyperbaric oxygenation, VC — vital capacity, GIT — gastrointestinal tract, MV — mechanical ventilation, IDH — infectious disease hospital, ARF — acute respiratory failure, CVA — cerebral vascular accident, ICU — intensive care unit, BFP — bacterial food poisoning

Introduction

Botulism is a serious infectious disease caused by bacterial toxin, known to humankind since ancient times. Historically, the name "botulism" comes from the Latin "*botulus*" — sausage — a product that previously caused botulism and where the pathogen was first isolated [1–3]. However, meat products are now a rare cause of botulism. In Moscow, for example, home-preserved mushrooms and vegetables are now the number one cause, followed by salted and smoked home-produced fish [2, 3].

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Epidemiology

The dangers of home canning are well known and obvious: the heat resistance of the spores allows them to withstand boiling for up to 6 hours, while the concentration of salts and vinegar used in canning does not prevent toxin formation, and the sealing of cans at home leads to the creation of anaerobic conditions. Toxin-containing canned foods do not change color, taste, or smell [1–3, 8]. Industrially manufactured canned food is relatively safe, since the technology of their production should provide for compliance with technical conditions and standards established by regulations in force in the state that adopted the standard [2, 6]. Toxin formation in home-produced canned products is uneven, that is, it occurs in "pockets", leading to selective infection of the people consuming said product, which corresponds to the literature [2, 3, 8, 9]. All of the above combined with the popularity of home canning explains the relatively high incidence of botulism worldwide. For example, in the Russian Federation about 300 cases of botulism are registered annually [2].

The introduction of therapeutic anti-botulinum serum (ABS) into clinical practice, the use of mechanical ventilation (MV), the use of hyperbaric oxygenation (HBO), the rational use of broad-spectrum antibiotics to prevent the activation of opportunistic microflora contributed to the improvement of patient outcomes and the reduction of the number of adverse outcomes in this disease [3–5]. Mortality from botulism according to the literature currently ranges from 7 to 9 % [2].

Pathogenesis

Seven serotypes of botulinum toxin — A, B, C, D, E, F and G — are known, but the disease in humans is mainly caused by three of them — A, B and E. Immunity after the disease is type-specific, so reinfection is possible [2, 3, 7, 9].

The incubation period is on average from 2–4 hours to 2–3 days, with maximum of 5 days, which almost always depends on the dose of the toxin.

Botulinum toxin with food enters the gastrointestinal tract (GIT) and penetrates into the neuromuscular synapses by hematogenous way. It has been proven that botulinum toxin selectively affects the motor neurons of the anterior spinal horns, motor nuclei of the cranial nerves and peripheral nervous system by stopping the release of acetylcholine from acetylcholine-containing bubbles. The block of nerve impulses transmission leads to myasthenia gravis and pseudo-paralysis without anatomical damage, which are restored when the toxin is neutralized. The cause of death in patients is respiratory arrest secondary to progressive acute respiratory failure (ARF) and cardiac arrest. The process of a patient's recovery is due to the gradual breakdown of the botulinum toxin in the places of its fixation, possible aspiration of vomit, the addition of secondary bacterial infection and ventilation hypoxia [2–5, 8].

Clinical course

Human botulism symptoms are specific and consist of several main syndromes: paralytic, gastrointestinal and intoxication. In 30–50 % of cases, the disease begins with gastrointestinal syndrome [1–3, 5, 8]. The onset of the disease with the appearance of nausea, vomiting, loose stool, dry mouth is often the basis for the diagnosis of acute intestinal infection (bacterial food poisoning (BFP), acute gastroenteritis, salmonellosis, etc.) or acute pathology of GIT (irritable bowel syndrome, exacerbation of chronic gastritis, acute pancreatitis, etc.). It is important to remember that the phenomena of gastrointestinal lesions in botulism are short-term (up to 1–2 days) and disappear by the time of the appearance of neurological symptoms [1–3]. Often the first signs of botulism are the patient's complaints of visual impairment (cloudy vision, diplopia, ptosis, inability to read the text), which is the cause of erroneous visit of patients to an ophthalmologist. There is also a need to differentiate botulism with true neurological pathology (cerebral vascular accident (CVA), encephalitis, myasthenia gravis, etc.). It is important to remember that the distinctive features of the paralytic syndrome in botulism are symmetry, bilaterality and the absence of sensitivity disorders [2, 4, 8].

It should be noted that the assessment of the severity of neurological symptoms is largely subjective and depends on the doctor's qualification, which can often cause errors in determining the true severity of the process.

Impaired swallowing of a liquid of any severity is recognized as a criterion of severe botulism. This symptom is easily determined by any practitioner with minimal knowledge of the epidemiological history of the disease and clinical signs. This criterion is an absolute indication for urgent hospitalization of patients in the intensive care unit, even bypassing the emergency department.

Complaints of patients on a feeling of not getting enough air, difficulty to inhale, dyspnea, the so-called "respiratory discomfort", regardless of the severity of other neurological symptoms, are also an indication for the administration of appropriate resuscitation treatment for the patient. It should be noted that external respiration disorder often occurs after the symptom of impaired swallowing of liquid. Thus, severe botulism is considered two states, when, regardless of the presence and severity of all other signs of botulism, dysphagia with liquid food and "respiratory discomfort" take place [2, 4].

Features of respiratory failure in patients with botulism

The development of ARF in patients with botulism is associated with paresis of the respiratory muscles, paresis of the abdominal muscles, soft palate and epiglottis. In turn, this can lead to impaired mechanism of coughing, getting saliva into the respiratory tract, and in some cases, aspiration of gastric contents in case of vomiting. Aspiration pneumonia occurs most often in patients with severe forms of botulism, but itself is rarely the cause of ARF [2, 4, 5, 8]. In addition, a number of patients with botulism have a high position of the diaphragm secondary to paresis of the gastrointestinal tract, which also aggravates the external respiration function.

Thus, ARF in patients with botulism develops by hypoventilation type, which complicates the differential diagnosis of ARF caused by other causes, clinical assessment of respiratory failure and the choice of therapeutic measures.

Treatment

All patients with suspected botulism are subject to mandatory hospitalization, since the development of ARF is possible. The primary task of the doctor at the prehospital stage is the quickest possible removal of the unabsorbed toxin from the patient's body by washing the stomach and intestines with a 5 % solution of sodium bicarbonate ($NaHCO_3$). Due to the danger of vomit aspiration in patients with impaired fluid swallowing, primary gastric lavage is carried out only by means of a gastric probe, in the volume of 2–3 liters.

The next stage of therapy is the introduction of anti-botulinum serum (ABS) to neutralize the circulating toxin in the blood as soon as possible from the onset of the disease [1–3]. Before the introduction of serum, blood should be sampled in the amount of 10 ml, as well as urine, gastric lavage liquid (vomit) for testing for botulinum toxin and the causative agent of botulism. A food product that is believed to have caused the disease is also sent for analysis. After diagnosis with an undetermined type of toxin, anti-botulinum serum with ABE types must be administered: type A — 10,000 U, type B — 5,000 U, type E — 10,000 U. In case of known type of toxin, monovalent serum should be used. One dose of serum is given, fractionally, according to the instructions dated 17.02.2000 (Besredka method). To avoid possible allergic reactions, 60-90 mg of prednisolone is administered to the patient prior to intravenous infusion of serum [1].

In addition to specific treatment, pathogenetic therapy is carried out to eliminate pathological changes caused by botulinum toxin, including secondary ones; detoxification therapy and proper care are provided [2, 3, 5, 7, 8]. Enteral nutrition through the nasogastric tube should be begun as soon as possible.

Due to the development of tissue hypoxia, hyperbaric oxygenation (HBO) should be included in the set of therapeutic measures whenever possible [2, 5].

Secondary bacterial complications are treated with antibacterial drugs.

The development of neurological lesions in botulism has a fairly clear direction "from top to bottom": vision impairment → difficulties with swallowing (solid food → liquid) → respiratory impairment, i. e. ARF occurs after the complete disappearance of the ability to swallow liquid. Therefore, all patients with aphagia (complete inability to swallow even liquids) are recommended routine nasotracheal

intubation [3, 4]. With nasotracheal intubation, the possibility of gastric content aspiration is excluded, the bronchoalveolar lavage is facilitated and it is possible to transfer the patient to MV in a planned manner, i. e. before the development of severe ARF events.

The experience of the authors of this work, accumulated in the management of patients with a variety of nosological forms, shows that nasotracheal intubation can be carried out for a long time (in our experience in the case of botulism — up to 81 days) without any severe side effects and allows to avoid a tracheostomy [5].

The final extubation is carried out only with the full restoration of liquid food fraction swallowing. Transfer of the patient to the general infectious department is carried out not earlier than 2–3 days after extubation.

Complications

Non-specific complications of botulism include various secondary microbial complications, among which pneumonia is distinguished both in the frequency of occurrence and in the influence on the outcomes of the main process [2, 5]. The combination of pneumonia with bronchitis, laryngitis and sinusitis is possible. Several complications in the urinary system (pyelonephritis, pyelitis, etc.) are less common. Also, botulism promotes the activation of any chronic inflammatory processes, especially in female genitals [1, 2]. In addition, with botulism, iatrogenic complications are often detected, which include all cases of drug allergy (and primarily serum disease), dysbiosis during prolonged use of antibacterial agents, post-injection infiltrates, abscesses, bedsores, etc.

Cardiac lesion in the form of myocardiodystrophy can be considered as a specific complication of botulism — botulinum myocarditis that occurs on day 7–15 of the disease [5]. The specificity of this process is confirmed by the direct relationship of its incidence with the severity of the main process (i. e., with toxin dose) and the absence of such with the presence of secondary microbial complications and/or the intensity of drug therapy (in particular — with doses of ABS), i. e. with purulent intoxication and nonspecific allergization [2, 5].

Procedure for discharge of patients from hospital

There are no clear terms of discharge of patients with botulism from the hospital, because they are strictly individual and depend only on the rate of reverse development of symptoms during the main process and the complications. It is believed that the patient can be discharged after complete recovery of swallowing, phonation and articulation, and complete resolution of the manifestations of secondary complications. At the same time, asthenic syndrome and moderate visual impairment (inability to read small print) may persist for several months (5–6) and are not indications for prolonged stay of patients in the hospital [3].

These data indicate the need for this work, the purpose of which is to assess the clinical course of botulism and analyze errors in diagnosis.

Materials and methods

The analysis of 27 medical records of patients diagnosed with botulism in IDH No. 1 for the period 2016–2017 was carried out. Statistical data processing was carried out using the standard STATISTICA 6.0 MS Office application package.

Study results and discussion

We have analyzed 27 medical records with diagnosis of botulism during 2016–2017. The mean age of the patients ranged from 30 to 87 years. Among the patients, 20 (74 %) were women. It should be noted that the majority of patients (67 %) were admitted to the hospital on the 4th–5th day of the disease and only 9 (33 %) patients were hospitalized before the 2nd day of the disease, which affected the severity of the course and the duration of hospitalization. At the initial visit for medical attention, botulism was diagnosed only in 8 patients, which amounted to 29 % of cases, another 8 patients were diagnosed with BFP, and 8 (29 %) more patients were hospitalized with suspected CVA. It was not possible to exclude alcohol intoxication in two patients, and 1 patient was hospitalized with the diagnosis of acute pancreatitis.

Based on the data of epidemiological history, it was found that in 13 patients (48 %) the disease was

associated with the use of home-preserved mushrooms, 5 (19 %) — smoked fish and 9 (33 %) — other home-produced canned products. Thus, the consumption of canned food and smoked products on the eve of the disease was noted in 100 % of patients, but only in 59 % it was revealed at the prehospital stage, and only in 41 % — on the 2nd-4th day from admission to the hospital, which led to an incorrect diagnosis.

It should be noted that all patients on the first day of the disease complained of nausea, weakness and dryness of oropharyngeal mucous. Most of the patients with complaints of visual impairment (gray fog, blurry vision, and double vision), weakness, hoarseness, dysarthria were examined by a neurologist on the first and subsequent days of hospitalization, but botulism was not suspected.

In 62.5 % of patients (5 patients out of 8) with primary diagnosis of CVA, previous gastrointestinal syndrome (nausea, vomiting, abdominal pain, loose stool) was not diagnosed, which caused erroneous diagnosis.

Two patients before hospitalization were examined by several specialists (ophthalmologist, surgeon and neurologist), which also did not allow timely diagnosis. The above data testify to insufficient knowledge of epidemiological history and symptoms of botulism among health care personnel that is required for early diagnosis of botulism.

Taking into account the criteria of primary disease severity, out of 27 patients, a severe course was reported in 13 (48 %), 5 patients had a mild course and 9 patients had a moderate course. Seventeen patients were hospitalized in the ICU, 13 of them required mechanical ventilation (MV). The duration of MV ranged from 4 to 55 days. Twenty-six patients were discharged with recovery. One fatal outcome in an 87-year-old female patient was due to late admission.

The diagnosis of botulism does not require 100 % laboratory verification of the diagnosis, and so the diagnosis is usually based on clinical and epidemiological data. All patients underwent gastric and intestinal lavage with the sampling of biological material to identify the toxin before ABS administration, and only 10 (37 %) patients had the diagnosis confirmed by laboratory tests. Type A toxin was detected in 6 patients, type B and E — in 2 patients, respectively. No complications of ABS administration were reported in any patient. Immediate administration of ABS is recommended for all patients with suspected or diagnosed botulism. The reason for refusal of serum administration can be only late admission of the patient with a clear reverse development of disease symptoms.

The above is confirmed by the following clinical cases.

Clinical case No. 1

Patient G., 58 years old, was delivered by the ambulance team to IDH No. 2 on 11.09.2017 with a diagnosis of acute gastroenteritis of unspecified etiology on the second day of the disease. From the epidemiological history it is known that on September 9 the patient ate home-produced smoked fish brought from Astrakhan. The next day he felt heaviness in his stomach, weakness, nausea; vomiting with eaten food occurred 5 times; and he noted a single episode of loose stool without pathological impurities. The patient self-induced vomiting, irritating the back wall of the oropharynx using two fingers, but the general state remained the same. On September 11, the patient called an ambulance and was hospitalized with diagnosis of acute gastroenteritis in IDH No. 2. On 12.09.2017 the patient's condition worsened; there were complaints of double vision, dry mouth, hypernasal voice, and, in this regard, the diagnosis of intestinal infection was withdrawn, and suspected botulism was the reason for the patient's transfer to IDH No. 1.

The state on admission was considered as severe. There are complaints of weakness, double vision, dry mouth, difficulties with liquid food swallowing. The patient has complaints of heaviness in the abdomen, hoarseness, and a feeling of not getting enough air. During examination the skin is pale. Respiratory rate is 16 breaths per minute. Bronchial breathing is auscultated in the lower parts. Pulse is rhythmic with satisfactory filling and tension, 70 beats per minute. Blood pressure is 125/70 mm Hg. Heart sounds are rhythmic without pathological sounds. Tongue is dry with white coating. During the examination of the oropharynx palatine velum sagging was visualized. During palpation, the abdomen is not distended and painless in all departments. Liver and spleen are not enlarged. Patient had no stool since 11.09.2017. Urination is free. Facial expressions are

preserved, there are bilateral hemiptosis of upper eyelids, bilateral mydriasis, and pharyngeal reflex is not triggered. The clinical diagnosis was severe botulism.

At the department, blood was taken for testing for botulinum toxin. In order to empty the stomach a nasogastric tube was introduced, and the washing was collected for laboratory testing. Also, the bowel was cleaned using a high enema with 5 % sodium bicarbonate. A single dose of polyvalent ABS (type A — 10,000 IU, type B — 5,000 IU, type E — 10,000 IU) was intravenously administered in accordance with the Guidelines 2000. The presence of aphagia and the risk of sudden respiratory arrest in patient were the reasons for the patient's transfer to the ICU with a nasotracheal intubation. MV was performed in the BIPAP mode taking into account physiological parameters.

The patient was prescribed detoxification therapy, and intravenous ciprofloxacin was administered at a dose of 0.4 g twice a day for 10 days to prevent complications caused by secondary bacterial flora. Enteral nutrition was carried out through the nasogastric tube until the restoration of independent swallowing. On September 19 (7 days of MV) after complete recovery of breathing and swallowing, the patient was extubated and two days later was transferred to the diagnostic department to the general ward. The set of therapeutic measures included 5 sessions of HBO. The patient was discharged on the 21st day of the disease (29.09.2017) in a satisfactory condition under the supervision of a primary care doctor.

This clinical case demonstrates the difficulties of botulism diagnosis at the prehospital stage. The onset of the disease with gastroenteritis symptoms was the basis for the diagnosis of intestinal infection of unknown etiology, and only the symptoms of paralytic syndrome that appeared from the 3rd day allowed to suspect botulism. The disease was regarded as severe, since there was aphagia, bulbar paralysis and impaired breathing.

Clinical case No. 2

Patient A., 48 years old, was transferred to IDH No. 1 from the neurological department of the therapeutic hospital on 04.12.2016 with a diagnosis of botulism.

From the epidemiological history, it is known that on December 2, he alone ate canned fish in a glass container, sausage, pork in a vacuum pack bought at a country fair.

Deterioration of general state occurred on the next day, 03.12.2016, when he felt discomfort in the abdomen, vomited twice, and had loose stool without pathological impurities — up to 6 times. He did not seek medical attention and did not take any medications. On the next day (December 4), he noted a decrease in visual acuity, double vision, slight weakness, dizziness. Loose stool did not appear. He visited the ophthalmologist in an outpatient department, who revealed paralysis of the medial rectus muscle of the right eye, and with suspected CVA the patient was sent for hospitalization in the neurological department of a therapeutic hospital in Moscow, where after examination, the diagnosis of ischemic stroke with bilateral gaze paresis and bulbar vestibulocerebellar ataxia raised doubts. The patient was examined by an infectious disease specialist who suggested botulism. After gastric lavage and enema with 5 % sodium bicarbonate, the patient was transferred to IDH No. 1 on the same day. Upon admission, the patient's condition was regarded as moderate, as there were complaints of double vision, dry mouth, dizziness, moderate general weakness. The gastrointestinal syndrome has regressed.

Examination results: skin is of normal color, clean, there are no edema and hemorrhages. With auscultation, breathing in the lungs is vesicular. Respiratory rate is 16 breaths per minute. Pulse is rhythmic with satisfactory filling, 68 beats per minute. Blood pressure is 120/80 mm Hg. Heart sounds are rhythmic without pathological sounds. Tongue is dry with white coating. Abdomen is moderately distended and painless during palpation in all parts. Liver and spleen are not enlarged. There was no stool during hospitalization. Urination is normal. Facial expressions are preserved, bilateral hemiptosis of upper eyelids, bilateral mydriasis, significant divergent strabismus, gaze paresis, the pharyngeal reflex is reduced. The state of consciousness was normal. Upon admission, the patient was immediately administered with one dose of polyvalent ABS (type A — 10,000 IU, type B — 5,000 IU, type E — 10,000 IU) in accordance with Guidelines for use of purified concentrated liquid anti-botulinum serums

with types A, B, C, E and F, approved on 17.02.2000. Adequate detoxification therapy was carried out in the patient, and intestinal stimulation was performed using enema with 5 % sodium bicarbonate. To prevent complications caused by opportunistic bacterial flora, Ceftriaxone at a dose of 1.0 g twice a day was intravenously administered for 10 days.

The patient was discharged in a satisfactory condition under the supervision of an infectious disease specialist at the place of residence on the 13th day of the disease.

In this clinical case, the incorrect interpretation of the paralytic syndrome in botulism and underestimation of the epidemiological history, which were the cause of the erroneous diagnosis of stroke, were demonstrated.

Summary

1. The knowledge of epidemiological history and clinical presentation of this disease will allow any physician in the shortest possible time to hospitalize a patient in an infectious diseases hospital to prevent death.
2. Impaired liquid swallowing of any severity indicates a severe course of the disease and is an indication for urgent hospitalization of the patient in the intensive care unit.
3. As specific therapy, all patients with botulism need intravenous administration of one dose of ABS according to the directions for use (fractional administration of serum by Besredka method).
4. Respiratory failure in botulism is manifested by a feeling of compression in the chest, impaired rhythm of breathing, difficulties in inhaling and exhaling due to damage to the respiratory muscles and diaphragm and has hypoventilation nature.
5. Efficacy of complex therapy in patients with severe botulism is affected by the maintenance of close psychological contact of medical staff with the patient, which is necessary to create optimism in the patient about the ongoing therapeutic measures.

Conclusion

Thus, despite the clearly expressed clinical pattern of botulism, a large number of diagnostic errors can be because the disease is relatively rare, doctors are not familiar with it and ignore the epidemiological history.

The clinical and epidemiological study, analysis of the literature data allowed to establish that at the prehospital stage, acute intestinal infection, acute cerebrovascular accident, hypertensive crisis, encephalitis, myasthenia gravis are most often diagnosed instead of botulism.

At the same time, the general practitioner must have the necessary and sufficient knowledge to timely suspect botulism, and should be able to provide emergency aid, since early diagnosis and timely pathogenetically justified treatment reduce the frequency of possible complications and deaths in botulism.

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DOI: 10.20514/2226-6704-2019-9-4-260-268 UDC 616.12-008.313.2-085.22

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THE USE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS IN THE PREVENTION OF ATRIAL FIBRILLATION

Abstract

Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders. Its prevalence is about 1 % in the general population and exceeds 7 % in individuals older than 60 years of age. It is known that hyperactivation of the renin-angiotensin-aldosterone system plays a key role in structural and electrical myocardial remodeling in AF. Increased activity of the renin-angiotensin-aldosterone system causes inflammation, fibrosis and oxidative stress in cardiomyocytes. Last studies suggest that most of negative effects previously explained by angiotensin-2 may be particularly caused by excessive aldosterone activity. More data about extra-adrenal hormone production (in the myocardium, the vascular wall and even the brain) have appeared, and its receptors were found far beyond the kidneys — in cardiomyocytes, endothelial cells, fibroblasts, monocytes, and macrophages. It was also shown that aldosterone has a wide profile of pathogenic effects, one of which is the stimulation of atrial myocardial fibrosis as the structural basis for AF. The discovery of new features of aldosterone suggests that blockade of mineralocorticoid receptors may prevent or slow down atrial remodeling and thereby reduce the incidence of AF. The article presents data of the world literature and the results of own studies devoted to the use of mineralocorticoid receptor antagonists in patients with AF. Modern concepts of the role of aldosterone in the arrhythmia development and the main approaches of upstream-therapy are described. The possibilities of using eplerenone and spironolactone in primary and secondary prevention of AF are discussed.

Key words: *aldosterone, renin-angiotensin-aldosterone system, atrial fibrillation, relapses, eplerenone, spironolactone*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 01.04.2019 г.
Accepted for publication on 19.06.2019 г.

For citation: Vatutin N. T., Shevelyok A. N., Taradin G. G. et al. THE USE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS IN THE PREVENTION OF ATRIAL FIBRILLATION. The Russian Archives of Internal Medicine. 2019; 9(4): 260-268. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-260-268

BP — blood pressure, ACE — angiotensin converting enzyme, ARBs — angiotensin II receptor blocker, AT — angiotensin, CI — confidence interval, LV — left ventricle, MCR — mineralocorticoid receptors, RAAS — renin-angiotensin-aldosterone system, EF — ejection fraction, AF — atrial fibrillation, CHF — chronic heart failure, BB — β-blockers

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Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders. Its incidence reaches 1 % in the general population and exceeds 7 % in individuals over 60 years of age [1]. The relevance of the problem with AF is dictated not only by the high rate of thromboembolic complications associated with it and deterioration of quality of life of patients, but also by a significant increase in the risk of general and cardiovascular mortality in patients with this arrhythmia [2].

Despite the progress made in understanding the electrophysiological mechanisms of the development and maintenance of AF, the pathogenesis of this arrhythmia remains understudied. It is known [3, 4] that hyperactivation of the renin-angiotensin-aldosterone system (RAAS) plays a key role in the development of structural and electrical myocardial remodeling underlying this arrhythmia. Higher activity of RAAS contributes to the development of inflammation, fibrosis, and oxidative stress in cardiomyocytes. Studies in recent years [5, 6, 7] suggest that most of the negative effects previously explained solely by the action of angiotensin-2 (AT-2) may be partly due to excessive activity of aldosterone.

Indirect evidence on aldosterone participation in AF development was obtained as early as 2005 by P. Milliez et al. [8], who showed that patients with primary hyperaldosteronism had a 12-fold higher risk of AF compared to the general population. Information concerning the role of aldosterone in the human body has undergone significant changes in recent years [9]: there is evidence on extra-adrenal hormone production (in the myocardium, the vascular wall and even the brain), and its receptors were found far beyond the kidneys — in cardiomyocytes, endothelial cells, fibroblasts, monocytes, and macrophages. At the same time, it was shown [10] that the hormone has a wide range of various pathogenic effects, one of which is the stimulation of atrial fibrosis, which is the structural basis for the development of atrial fibrillation.

Previously, it was believed that the use of angiotensin-converting enzyme (ACE) inhibitors leads to persistent inhibition of aldosterone synthesis by blockade of RAAS [11]. It was later revealed that the decreased production of this hormone during therapy with ACE inhibitors is short-term, and then its concentration in the blood increases again due to the effect of the hormone escaping drug control [12]. According to some studies [5], even a combination of ACE inhibitors and angiotensin-2 receptor blockers (ARBs) is not able to adequately suppress the production of aldosterone. This is due to the availability of alternative, non-AT-2-related stimuli for its formation. It has also been proven that aldosterone is just one of several hormones linking to mineralocorticoid receptors (MCR). In some diseases, such as chronic heart failure (CHF), hypertension, acute myocardial infarction, diabetes, activation of MCR can occur under cortisol action, which in normal conditions does not have a similar effect [13].

Thus, the discovery of new features of aldosterone suggests that the blockade of MCR can prevent or slow down atrial remodeling and thus contribute to decreased AF incidence.

Currently, the use of various antiarrhythmic drugs remains the cornerstone of anti-relapse therapy for AF [14–16]. However, this strategy does not always yield the expected results: first, antiarrhythmic drugs are usually prescribed after the first episode of AF, when its substrate is already, as a rule, formed; secondly, they affect only electrophysiological processes in the myocardium (duration of the action potential and the rate of the excitation pulse), without affecting the structural substrate of arrhythmia [15]. In addition, the use of antiarrhythmic agents in order to preserve the sinus rhythm is limited by their weak efficacy and the possible development of serious side effects.

Therefore, today the attention of researchers is increasingly focused on the so-called drugs for upstream-therapy, which are able to prevent the occurrence of AF, affecting its substrate. Such drugs include ACE inhibitors, ARBs, statins, omega-3 polyunsaturated fatty acids and MCR antagonists [17–20]. Their antiarrhythmic effect is caused by several factors: prevention of structural atrial remodeling by suppressing the processes of fibrosis, inflammation and oxidative stress, improving hemodynamics by reducing blood pressure (BP) and tension of the walls of the heart chambers, as well as preventing the development or progression of coronary artery disease, which is known to be one of the most important risk factors for AF [21].

A number of studies [22–26] have shown that the use of ACE inhibitors and ARBs prevents the development of new AF cases. Retrospective analysis in SOLVD (Studies of Left Ventricular Dysfunction) [22], which included 391 patients with left ventricular (LV) ejection fraction (EF) less than 30 %, showed that the use of enalapril reduced the risk of AF from 24 % to 5.4 %, and also reduced mortality in such patients. In another large study [23], which included 1,577 patients with left ventricular systolic dysfunction which developed as a result of myocardial infarction, the use of trandolapril within 2–4 years after the onset of infarction reduced the AF rate by 55 % (hazard ratio (HR) of 0.45; p <0.01). In the Val-HeFT (Valsartan Heart Failure Trial) study [24], the addition of valsartan to standard CHF therapy resulted in a 37 % decrease in AF rate. In a large LIFE (Losartan Intervention For End Point Reduction in Hypertension) study [25], 9,193 patients with hypertension and LV hypertrophy without AF were randomized into 2 groups: in group 1 they took losartan (50 mg/day), in group 2 — atenolol (50 mg/day) as antihypertensive therapy for an average period of 4.8 years. Despite an equal decrease in BP, the rate of AF paroxysms when taking losartan was significantly lower and amounted to 6.8 cases per 1,000 people per year, whereas when receiving atenolol it was 10.1 cases (HR of 0.67; p <0.001). The incidence of stroke among patients with AF paroxysms was also significantly lower in the losartan group (HR of 0.49; p = 0.01).

The results of the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study [26] involving 15,245 patients with hypertension, where valsartan reduced the risk of new AF cases by 17 % and of persistent AF — by 32 % compared to amlodipine, are convincing.

However, the positive role of ACE inhibitors and ARBs in secondary AF prevention is unfortunately questionable. A large randomized placebo-controlled GISSI-AF [27] study investigating valsartan efficacy for secondary prevention of AF paroxysms showed that the use of this drug for 1 year was not associated with a decrease in the rate of repeated AF episodes. There was no effect of valsartan on secondary endpoints — the number of arrhythmia episodes, heart rate at the first repeated episode, the number of hospitalizations for all reasons. The results of the J-RHYTHM II study did not demonstrate the advantages of candesartan in comparison with amlodipine for the prevention of repeated AF cases during 1 year [28].

Data on the efficacy of these drugs in the prevention of AF and in patients without pronounced structural changes of the heart are not convincing. The ANTIPAF study, which evaluated the possibility of using ARBs for secondary prevention of AF in patients with no pronounced structural changes of the heart, did not reveal a significant difference in efficacy between olmesartan and placebo [29]. Retrospective analysis of the AFFIRM study as a whole did not demonstrate the advantages of RAAS-blocking drugs for the control of sinus rhythm, but revealed their efficacy only in patients with CHF [30].

Apparently, the use of ACE inhibitors or ARBs is effective only in reducing the rate of new AF cases. Adding them to standard antiarrhythmic drugs in patients with existing AF does not increase the chances for maintaining sinus rhythm.

Some researchers [30] explain the lack of effect of these drugs in the secondary AF prevention by the already formed arrhythmia substrate, on the one hand, and the insufficient period of treatment for the implementation of the positive drug properties, on the other hand. Another possible explanation lies in the effect of aldosterone escape: apparently, the use of only ACE inhibitors or ARBs is not enough for a complete blockade of RAAS.

Numerous evidence of the important role of aldosterone in atrial remodeling and AF development [7, 31, 32] suggests that the use of MCR antagonists may prevent the occurrence of new cases or recurrence of this arrhythmia.

Indeed, a lot of experimental data have been accumulated [33–37] on the beneficial effect of MCR antagonists on the processes of structural atrial remodeling. In experimental models of permanent AF, spironolactone reduced the severity of cardiomyocyte apoptosis, cell degeneration, atrial fibrosis and contributed to the maintenance of functional parameters, in particular, LV EF [35]. These data clearly show that the blockade of MCR is a powerful therapeutic strategy and in combination with the use of ACE inhibitors or ARBs can contribute to the preservation of atrial structure and function with AF.

In another experiment [38] preliminary administration of eplerenone prevented excessive activation of profibrotic agents, but led to a subsequent increase in the level of AT-1. At the same time, additional use of losartan prevented aldosterone-mediated atrial fibrosis.

It is reported [39] that aldosterone has a powerful proinflammatory effect on myocardium, vessels and kidneys, while MCR blockers have pronounced anti-inflammatory properties.

Thus, experimental studies confirm the view that MCR blockade in combination with AT-2 inactivation can prevent the development of structural atrial remodeling and AF occurrence. However, the results of clinical studies on this issue are few and contradictory [40].

Eplerenone in AF prevention

Eplerenone is a relatively selective MCR blocker, binding mainly to these receptors, and to a lesser extent — glucocorticoid, progesterone and androgenic receptors [41]. The efficacy of eplerenone in AF prevention is confirmed in several studies.

In CHF. Ventricular dysfunction occurring in CHF is one of the main factors of structural and electrophysiological atrial changes underlying AF. Eplerenone has demonstrated its efficacy in AF prevention in patients with CHF. A two-year prospective EMPHASIS-HF study [42] investigated the use of eplerenone in patients with confirmed CHF of II functional class with reduced LV EF (≤35 %), who were on therapy with RAAS blockers (96.5 %) and -blockers (BB) (86.7 %). The use of eplerenone as the third neurohormonal modulator for an average of 21 months was accompanied by a decreased rate of new AF cases by 42 % (p = 0.034).

In hypertension. About 70 % of patients with AF have hypertension. Having a hypotensive effect, aldosterone antagonists can contribute to better control of BP — the most important risk factor for AF. Currently, a multicenter cohort study is being conducted to assess the prevalence of primary aldosteronism among patients with hypertension and AF, as well as the role of specific treatment in the incidence of AF relapses [43].

In stable AF. The efficacy of eplerenone in maintaining sinus rhythm after catheter ablation in patients with persistent AF was studied. The results of the study [44] involving 161 patients with a long history of persistent AF (stable AF lasting from 1 year to 20 years, an average of 3.4±3.8 years) who underwent catheter ablation are presented. All patients received conventional drug therapy with ACE inhibitors or ARBs, and eplerenone was additionally administered for 55 patients. During the next 24 months of follow-up, AF relapse was detected in 47 %. In the eplerenone group, there were significantly more patients with persistent sinus rhythm (60 %) compared to the standard therapy group (40 %, p = 0.011). Analysis using multivariate Cox regression model showed that the long duration of AF (>3 years, p <0.001) and early relapses (p <0.001) significantly correlated with the rate of repeated arrhythmia episodes, and only eplerenone therapy was associated with the preservation of sinus rhythm after catheter ablation (p = 0.017).

The role of spironolactone in AF

Data on the efficacy of nonselective MCR antagonist, spironolactone, in the literature are few. A small open prospective randomized trial of SPIR-AF [45] included 164 patients with a history of AF at least 4 years ago, who were divided into 4 groups depending on the treatment prescribed: spironolactone (25 mg/day) plus BB plus enalapril, spironolactone plus BB, enalapril plus BB and only BB. The recurrence rate of AF was significantly lower in the groups of patients treated with spironolactone than in those whose treatment was limited only to BB or a combination of the latter with enalapril.

In another randomized study [46] involving 166 patients with CHF, the use of spironolactone for 6 months was associated with a lower risk of new AF cases.

Disappointing results were obtained in a study on the role of ramipril and spironolactone in the prevention of postoperative AF in patients undergoing coronary artery bypass grafting [47]. Patients of the main groups for 4–7 days before surgery were administered with ramipril at a dose of 2.5–5.0 mg/day or spironolactone 25 mg/day, and patients in the control group received a placebo. Each group consisted of approximately 150 people. Treatment continued until discharge from the hospital.

Neither ramipril nor spironolactone showed significant differences in the rate of postoperative AF compared to the placebo. It can not be excluded that the lack of effect of these drugs is due to their isolated intake. Perhaps a combination of two RAAS inhibitors is necessary for successful prevention of AF.

We conducted our own study [48], which aimed to assess the efficacy and safety of spironolactone used in addition to standard therapy in patients with recurrent non-valvular AF. The work was carried out in accordance with international standards of GCP and the requirements of the Helsinki Declaration. The study protocol and informed consent form for patients were approved by the local Ethics Committee, Institute of Emergency and Reconstructive Surgery n. a. V. K. Husak (minutes of meeting No. 11 dated 23.09.2013).

A prospective cohort open-label randomized trial was performed in 89 patients who were included with an AF episode. After restoration of sinus rhythm all patients were randomized into 2 groups: individuals in group 1 (n = 46) continued to receive standard drug therapy (ACE inhibitors/ARBs, β-blockers, statins, antithrombotics, antiarrhythmic drugs of class III), patients in group 2 (n = 43) additionally received spironolactone at a dose of 25 mg/day with subsequent titration up to 50 mg/day. The duration of treatment and follow-up was 6 months, with the primary endpoint being a relapse of AF. The secondary endpoints of the study were the time before the first arrhythmia relapse, the type of sinus rhythm restoration (spontaneously or using cardioversion), the method of cardioversion (electrical, pharmacological), changes in the structural and electrophysiological parameters of the myocardium, and the development of adverse events.

Before treatment, there were no significant differences in age, gender, severity of underlying cardiac disease, comorbid conditions, left ventricular ejection fraction, volume of the left atrium and blood aldosterone between groups (Table 1).

The duration of AF history, number and predominant type of arrhythmia episodes, EHRA score, type and dose of antiarrhythmic drugs also did not differ between groups (Table 2).

Table 1. *Initial clinical characteristics of patients (m±σ, Me (Q1; Q3))*

Parameter	Control group (n = 46)	Spironolactone group (n = 43)	Significance (p)
Age, years, m±σ	62 (56; 69)	61 (55; 69)	0.9
Male, number of patients (%)	20 (44)	19 (44)	0.885
Hypertension, number of patients (%)	46 (100)	43 (100)	1.0
Heart failure I class (NYHA), number of patients (%)	12 (26.1)	10 (23.3)	0.95
Heart failure II class (NYHA), number of patients (%)	24 (52.2)	20 (46.5)	0.749
Heart failure III class (NYHA), number of patients (%)	10 (21.7)	13 (30.2)	0.5
LV EF, %	57 (52; 64)	56 (53; 63)	0.72
LA volume index, ml/m^2	28.6±4.4	29.0±5.1	0.94
Exertional angina, number of patients (%)	26 (56.5)	25 (58.1)	0.95
Exertional angina II class, number of patients (%)	16 (34.8)	14 (32.6)	1.0
Exertional angina III class, number of patients (%)	10 (21.7)	11 (25.6)	0.86
Myocardial infarction, number of patients (%)	32 (69.6)	32 (74.4)	0.786
Smoking, number of patients (%)	14 (30.4)	13 (30.2)	0.835
Diabetes mellitus, number of patients (%)	9 (19.6)	8 (18.6)	0.878
Body mass index, kg/m^2	32.1±4.8	31.8±5.2	0.95
Serum aldosterone during AF episode, pg/ml	172 (156; 198)	174 (155; 194)	0.748
Serum aldosterone level after sinus rhythm restoration, pg/ml	150 (132; 168)	148 (134; 165)	0.95
hsCRP serum level, mg/ml	4.22±0.78	4.18±0.64	0.9

Note: AF — atrial fibrillation, hsCRP — high sensivity C-reactive protein, LA — left atrial, LV EF — left ventricular ejection fraction

Table 2. *AF pattern and management in patients (m±σ, Me (Q1; Q3))*

Parameter	Control group (n = 46)	Spironolactone group (n = 43)	Significance (p)
Duration of AF anamnesis, months	24.2±6.2	22.8±4.3	p = 0.34
Number of registered episodes during the last 6 months	3 (2; 4)	3 (2; 4)	p = 1.0
Predominantly paroxysmal form of AF (spontaneous restoration of sinus rhythm), number of patients (%)	18 (39.1)	15 (34.9)	p = 0.847
Predominantly persistent form of AF (cardioversion is required for restoration of sinus rhythm), number of patients (%)	28 (60.9 %)	28 (65.1 %)	p = 0.847
EHRA II class, number of patients (%)	26 (56.5)	25 (58.1)	p = 0.953
EHRA III class, number of patients (%)	20 (43.5)	18 (41.9)	p = 0.953
Treatment with amiodarone, number of patients (%)	32 (69.6 %)	29 (67.4 %)	p = 0.991
Amiodarone average daily dose, mg	200 (200; 200)	200 (200; 200)	p = 1.0
Treatment with sotalol, number of patients (%)	14 (30.4 %)	14 (32.6 %)	p = 0.991
Sotalol average daily dose, mg	120 (80; 160)	120 (80; 160)	p = 0.934

Note: AF — atrial fibrillation

All patients received adequate concomitant drug therapy in accordance with current standards, there were no differences in the therapy between the groups. The mean dose of spironolactone in patients of group 2 at the end of the study was 37.5 (25; 50) mg/day.

For 6 months of treatment, relapses of AF were reported in 33 (71.7 %, 95 % confidence interval (CI) of 57.6 to 84.0 %) patients in group 1 and 21 (48.8 %, 95 % CI of 33.7 to 64.0 %) patients in group 2 ($\chi^2 = 3.97$; $p = 0.046$). At the same time, the absolute risk of arrhythmia relapse decreased by 22.9 % during additional spironolactone administration (95 % CI of 2.6 to 40.8 %, $p = 0.048$). Total time of follow-up was documented for 128 of arrhythmia relapses in group 1 and for 67 — group 2. The number of episodes per patient in group 2 was significantly ($p < 0.05$) lower compared to group 1 (2 (1; 2) versus 3 (2.5; 4), and the time before the development of the first relapse, on the contrary, was longer (62 (45; 78) days versus 32 (21; 45) days). Patients taking spironolactone had a higher number of cases with spontaneous sinus rhythm restoration compared to patients received standard therapy (35.8 % and 16.4 %, respectively, $\chi^2 = 8.28$, $p = 0.004$). The mean duration of AF relapse did not differ significantly between the groups.

In order to identify the pathogenetic mechanisms of spironolactone antiarrhythmic effect, we analyzed its effect on the main clinical and laboratory determinants of the disease. For 6 months of treatment, patients of group 2 showed a significant ($p < 0.05$ compared to baseline values and $p < 0.05$ compared to group 1) reduction of LV hypertrophy signs (thickness of the interventricular septum, LV myocardium mass index) and improvement of diastolic LV function (reduction in E/Em). LV myocardium mass index was also decreased in group 1, but this decrease was less pronounced than in group 2.

Positive changes during the follow-up period was noted in some indicators of myocardium electrophysiological state. Thus, patients in group 2 showed a significant ($p < 0.05$) decrease in the mean daily number of supraventricular and ventricular premature beats, dispersion of the P-wave and the registration rate of late atrial potentials.

Experimental studies show that aldosterone has a proinflammatory effect on myocardium, vessels and kidneys, while MCR blockers have pronounced anti-inflammatory properties. However, there are virtually no similar data obtained in clinical studies. We analyzed the effect of spironolactone on blood highly sensitive C-protein, a universal marker of inflammation. The baseline level of this protein did not differ significantly between groups. After 6 months of therapy, no significant changes in its concentration were observed in any of the groups.

The question about the effect of specific therapies with MCR antagonists on blood aldosterone is

of particular interest. Initially, this indicator did not differ between groups. The use of spironolactone for 6 months led to a decrease in the concentration of the hormone from baseline level (from 148 (134; 165) pg/ml to 124 (98; 138) pg/ml, p <0.05 compared to baseline values and p <0.05 compared to group 1). At the same time, in patients of group 1 who did not receive MCR antagonists, aldosterone level, on the contrary, increased significantly (from 150 (132; 168) pg/ml to 164 (146; 178) pg/ml, p <0.05).

During spironolactone administration, the frequency of adverse events requiring treatment discontinuation (hyperkalemia, orthostatic hypotension) was 12 % (95 % CI of 4.4 to 22.6 %). We did not observe any significant renal impairment and increased risk of gender-related side effects during 6 months of drug administration.

Thus, the use of spironolactone for 6 months as part of antiarrhythmic therapy was associated not only with significant reduction in the risk of AF relapses, but also with regression of LV hypertrophy, improvement in diastolic function, a decrease in the dispersion of the P-wave, ectopic atrial and ventricular activity and in the incidence of late atrial potentials. Our study did not reveal obvious effects of spironolactone on the volume of the left atrium and markers of inflammation: the decrease in these indicators during drug therapy did not reach statistical significance. It is noteworthy that the use of spironolactone for 6 months was associated with a decrease in plasma aldosterone, while the lack of MCR blockade led to its progressive increase, apparently due to the effect of the escape of aldosterone from therapy with ACE inhibitors and ARBs.

Currently, a randomized placebo-controlled INSPIRE-AF study (Inhibition of Aldosterone to Reduce Myocardial Diffuse Fibrosis in Patients with Paroxysmal and Persistent Atrial Fibrillation) is being conducted to assess the efficacy of spironolactone taken at a dose of 25 mg/day for 12 months in patients with paroxysmal and persistent AF with preserved LV EF [49]. The primary endpoint of this study is the reduction of myocardial fibrosis, determined by magnetic resonance imaging. The effect of the drug on the rate of AF relapses, quality of life of patients and laboratory markers of collagen metabolism will also be evaluated.

Currently, the study IMPRESS-AF (Improved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation), dedicated to the assessment of spironolactone effect on exercise tolerance, quality of life and diastolic function of the heart in patients with symptomatic AF and preserved LV EF is on active phase [50]. This study involves 250 patients, who were randomized to receive spironolactone at a dose of 25 mg/day or a placebo for 2 years. Interestingly, the study includes patients with permanent AF. The primary endpoint is an improvement of exercise tolerance after 2 years of follow-up. Secondary endpoints include changes in quality of life (according to EQ-5D and the Minnesota Living with Heart Failure Questionnaire), LV diastolic function, and hospitalization for any reason.

Thus, the role of aldosterone antagonists in AF has not yet been definitively determined. Further clinical studies will determine the need to include this group of drugs in the treatment protocols for patients with AF.

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DOI: 10.20514/2226-6704-2019-9-4-269-279 UDC 614.254.3:613.71

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PRIMARY CARE: HOW TO INCREASE PHYSICAL ACTIVITY IN YOUR PATIENTS

Abstract

Sedentary lifestyle, being a behavioral risk factor for chronic non-communicable diseases, is relevant for preventive medicine. A key role in the correction of behavioral risk factors for chronic non-communicable diseases is occupied by general medical practice, where the patient is continuously observed for many years. Increased physical activity reduces the risk of atherosclerosis, diseases of the musculoskeletal system, malignant tumors, has a positive effect on the psychological state of patients and reduces the overall morbidity and mortality. Increasing the reserves of the cardiorespiratory system of the body, physical activity improves the quality of life of patients and reduces the cost of medical care.
To effectively combat sedentary lifestyle, it is necessary to adequately motivate patients that can be achieved through routine counseling to enhance physical activity. The method of such consultation should take into account limited time of outpatient admission and all personal characteristics of patients (starting level of physical activity, health group and risk of disease).
The article presents a summary of modern scientific views in the field of increasing physical activity of patients, discusses current issues of counseling. The groups of patients with or without chronic diseases and the high risk of cardiovascular complications were discussed. The variant of rational outpatient counseling with the help of the algorithm of organization of physical activity mode, providing stratification of patients, planning, optimization and control of personal motor activity was presented. The proposed method of optimization of counseling successfully solves the problems of motivation, increase of physical activity and individual approach in outpatient practice.

Keywords: *physical activity, counseling, general medical practice*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 13.03.2019 г.
Accepted for publication on 23.05.2019 г.

For citation: Slobodyanyuk A. L., Krylova I. A., Kupaev V. I. PRIMARY CARE: HOW TO INCREASE PHYSICAL ACTIVITY IN YOUR PATIENTS. The Russian Archives of Internal Medicine. 2019; 9(4): 269-279. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-269-279

CHD — coronary heart disease, MI — myocardial infarction, CS — cerebral stroke, DM — diabetes mellitus, CVD — cardiovascular diseases, PA — physical activity, PE — physical exercises, RF — risk factors, NCD — non-communicable diseases

Today, the main cause of death is complications of non-communicable diseases (NCD), the cause of occurrence and development of which are behavioral risk factors (RF) [1, 2, 3]. The world health organization, among such RF of premature mortality in global population, put low physical activity (PA) on the fourth place [4]. In the presence of sedentary lifestyle, the risk of death from all causes increases by 20–30 % [1, 5], with cardiovascular diseases (CVD) among the primary causes: the risks of hypertension increase by 35–53 %, coronary heart disease (CHD) — by 30 %, diabetes mellitus (DM) —

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by 27 %, breast and colon cancer — by 21–25 % [5–9]. In Russia, about 40 % of the adult population have low PA [4, 5], which negatively affects workforce productivity and working life expectancy, and consequently, public health and social and economic situation [10], increasing direct and indirect costs of health care [10, 11]. When eliminating sedentary lifestyle, the life expectancy of the population will significantly increase [10, 12, 13]. At the same time, adequate physical exercises (PE) is recognized as an important factor in the prevention and treatment of NCD regardless of their stage [4, 14].

Correction of behavioral RF is carried out in the form of systematic and long-term tasks with the help of preventive counseling. In the presence of NCD, an individual plan to increase PA is drawn up, taking into account the individual clinical pattern, risks and ability to perform exercises [5]. General practitioners (family doctors) are the leading specialists in the field of personalized medicine, who are extremely immersed in the details of the clinical state, social, economic and cultural situation of their patients and their families [15, 16] and can most effectively solve the problems of adequate PA enhancement. In the process of step-by-step preventive counseling, they can use individual fitness trackers of the patient (bracelet or clip with built-in physical activity sensor, fitness watch with pulse monitor or heart rate monitor, pocket fitness trackers and/or smartphones) for individual daily monitoring of physical exercises.

PA and atherosclerosis

When implementing the tasks of increasing PA, positive metabolic changes occur, first of all, serum lipid profile: the levels of total cholesterol, low-density lipoproteins and triglycerides are reduced, the concentration of anti-atherogenic cholesterol, high-density lipoproteins is increased. Thus, regular PA reduces the risk of atherosclerosis [17–20].

Adequate PE have a positive effect on carbohydrate metabolism: reduce carbohydrate tolerance, increase tissue sensitivity to insulin, reduce the risk of hyperinsulinemia, insulin resistance and type 2 DM [21, 22]. Impaired carbohydrate metabolism and development of type 2 DM accelerate the development of atherosclerosis and its complications, and PA, improving carbohydrate metabolism, reduces the risk of atherosclerosis and related diseases [14–24]. The influence of aerobic exercises on the reduction of adiponectin with low molecular weight and insulin in blood serum has been proved [25].

PE, by reducing fibrinogen level, activity of VII factor and platelet aggregation, have a beneficial effect on rheological properties of blood and, thus, reduce the risk of thrombotic complications, such as myocardial infarction (MI) and/or cerebral stroke (CS) [18–20, 26, 27]. Current studies have convincingly shown that aerobic PE improve myocardial perfusion by dilation of coronary arteries, improve microcirculation and endothelial function [27, 28]. Regular PE improve the balance of energy consumption and capacity, which prevents the development of obesity. Excess weight and, especially, abdominal obesity contribute to the accelerated development of atherosclerosis. Thus, PA contributes to the normalization of body weight, reduction of abdominal obesity and, consequently, reduces the risk of atherosclerosis [19, 29].

PE regulate vegetative balance inducing ischemic preconditioning [30, 31], which in turn reduces the probability of myocardial damage and the risk of dangerous ventricular tachyarrhythmias, increasing the risk of sudden death [29, 31].

There are convincing data on the modification of the health status of patients with CVD performing PA in cardiac rehabilitation: cardiovascular mortality decreased by 30 %, mortality from all causes — by 20 %, the risk of re-MI — by 17 %, the need for hospitalization — by 60 % [27, 28, 32].

Aerobic PE can be objectively measured and strictly dosed, which increases safety and makes it possible to use them in different categories of patients, especially in the presence of CVD. Cardiorespiratory training, in comparison with simple aerobic PA, reduces the risk of cardiovascular complications — CHD and CS — almost two-fold [32].

PA and cancer

A number of studies have shown that the risk of developing cancer of different localization, in particular, breast and colon, decreases in the presence of an active lifestyle [5–9, 33–36]. PA in combination with a proper diet (stewing versus deep frying)

reduces the risk of breast cancer [37] and prostate cancer [38, 39] and plays a primary role in their prevention [37, 40]. The interrelation of cancer and the presence of systemic inflammation signs is proved. In this case, aerobic exercise improves the profile of inflammatory cytokines in adipose tissue, reducing the concentration of proinflammatory (IL-12p70, TNF-α, IL-6) and anti-inflammatory (IL-10) cytokines in inguinal and epididymal white or brown adipose tissue. However, moderate continuous aerobic exercises have no effect on the expression of lipolytic and thermogenic genes in adipose tissue [24, 25, 39, 41, 42].

PA and diseases of the musculoskeletal system

Regular PE lead to an increase and strengthening of muscle mass, improvement of neuromuscular activity, which reduces the risk of arthritis. The results of the studies did not confirm the common opinion that the risk of arthritis or traumatic joint damage increases during PA [10, 26]. As a result of carefully conducted statistical analysis, it was found that athletes who have been running for a long time, do not have more problems with the joints than people of the same age with a sedentary lifestyle. That is why the American Arthritis Foundation recommends PE in terms of flexibility and muscle strength training as an important component of therapy in patients with arthritis [26, 43].

Regular PE contribute to an increase in bone mineral density, reduce the rate of bone calcium loss, preventing the development of osteoporosis [43–45]. Analysis of the results of several studies showed that in the presence of PA, the risk of bone fracture, including the hip joint and spine, was reduced [45].

PA and psychological state of a person

These studies show that in the presence of physical activity, well-being and mood are determined much more often than in sedentary lifestyle, in addition, patients with greater physical activity are less prone to stress and depression [46]. Physical activity increases subjective assessments of well-being, perception of health and feeling of personal happiness [47].

PA and overall morbidity and mortality

Regular PE reduces the risk of developing major NCD: CVD — 40 %, CS — 27 %, type 2 DM — 58 %, Alzheimer's disease — 40 %, rectal cancer — 60 % or more, lung cancer — 20–24 %, recurrence of breast cancer — 50 %, the risk of falls in the elderly — 30 % and prevents depression and obesity [5–9, 37, 44, 45, 48]. In combination with sedentary lifestyle with mild cognitive impairment after 12-month aerobic exercise of moderate and high intensity, the indicators of neurocognitive functions improve in terms of memory, attention, fluency, information processing speed and executive functions, which are significantly associated with an increase in the circulation of B- and T-lymphocytes (CD4+ and CD8+) and a decrease in beta-amyloid, indicating a complex relationship between the adaptive immune system, PA and the carrier of the apolipoprotein E gene [49]. Adequate PE contribute to the normalization of lifestyle and social activity, in particular, skilled ability to work [1, 2].

It should be noted that PE have a dose-dependent effect, reducing the risk of coronary problems in a healthy population and in the presence of RF, or in patients with CVD of any age and gender. At PA with duration >30 min/week the relative risk of MI was 0.92 (95 % CI 0.67–1.28), and at PA >210 min/week — 0.71 (95 % CI 0.63–0.79), i. e. the degree of relative risk reduction increased from 8 % to 29 %, respectively [1, 2, 5, 11–13, 17].

Regular increase in PA reduces mortality from all causes: at PA <150 min/week the decrease in relative risk was 21 % (p <0.001), at FA 150–300 min/week — 34 % (p <0.001) and at PA >300 min/week — 46 % (p <0.001) [5, 10–13].

Risks associated with an increase in PE

In some cases, with the latent course of CVD, an increase in PE may increase the risk of sudden cardiac death. The number of such cases related to PE is 1:360,000 hours of running or 1:565,000 hours of PA (American Heart Association). At the same time, in 40 % of cases, these are patients with obvious or latent CVD, increasing PE without prior medical examination. In healthy people, the risk of serious

cardiovascular complications associated with PE ranges from 1:500,000 to 2,600,000 patient-years of exercise. The probability of developing cardiovascular complications during PE activities in terms of cardiac rehabilitation under the supervision of medical workers is 1:50,000 to 120,000 patient-years of exercise; sudden cardiac death — 1:340,00 0 to 750,000 patient-years of exercise [46].

With a careful, gradual increase in the level of PA, the right choice of the PA type, given the paramedical characteristics of the family (social and economic, cultural traditions, living conditions, the nature of interaction in the family, etc.) and careful implementation of programs to increase PA risk of adverse events is significantly reduced. If there is a risk of injury in PA types where such risk exists (e. g. cycling), it is recommended to use personal protective equipment such as helmets [29].

In general, prevention and rehabilitation plans have proven the efficacy and safety of PE: the mortality rate in the regular PA is 40 % lower in comparison with persons with a sedentary lifestyle [29, 32, 46].

Thus, at present, there are sufficient grounds to assert that the use of adequate PA is effective and safe with a careful, consistent increase in exercise intensity and the selection of PA type.

Absolute contraindications for the beginning or continuation of PA are:

- exacerbation of the underlying disease,
- unstable clinical condition,
- acute infectious diseases,
- pregnancy (women exercise according to special programs),
- the presence of symptoms that are suspicious in relation to CVD or other diseases (full examination, including a test with PE, is needed).

Those with the history of acute vascular or coronary events, who have serious complications and individual indications and contraindications, need personalized programs of long-term physical rehabilitation [27, 28, 30, 32, 50].

Psychological aspects of behavioral nature

Risk factors for NCD (unbalanced diet, smoking, alcohol consumption, sedentary lifestyle) are often associated with pleasure and rest, so recommendations to increase PA are often perceived by the patient as "deprivation of these pleasures" and therefore ignored [1].

Many factors influence the (non)implementation of PA recommendations: level of education, social status, nature of work, presence or absence of chronic diseases, age, etc. Therefore, recommendations for the optimization of PA should be adapted to a particular patient, taking into account the above factors. When consulting, it is desirable to focus on the individual benefits of PA for a particular patient (what they will get in return for the time spent on PA) [46, 49].

We can expect to improve the quality of life by increasing PA at any age.

It should be borne in mind that sometimes patients with sedentary lifestyle try to compensate for insufficient PA by excessive PE during rest days. This approach is especially dangerous, because it violates the principle of a gradual increase in volume and intensity of PE, and it can be a cause of severe complications of existing diseases in untrained patients. The key to health and longevity is only a rational, scientifically based training regimen. In addition, forms of active rest are less effective in terms of improving physical performance, since their task is to relieve industrial fatigue by using low-intensity and short-duration PA during the working day [46].

Only PA and PE, organized in a certain system of physical training, expand the reserves of the cardiovascular and respiratory system, modify RF of NCD, suppress the markers of atherothrombogenesis and thus prevent the development of NCD and their complications.

Correction of behavioral RF and, in particular, increase in PE is effective only with a gradual approach — step-by-step, better under the supervision of a general practitioner who can perform dynamic monitoring of the patient and conduct regular preventive counseling to correct existing behavioral RF of NCD [15, 16].

Outpatient counseling to improve PA

The low motivation of the patient to increase PA is due to many reasons, in particular, lack of understanding of PE benefits and/or unwillingness to implement them independently. In such

a situation, the primary task is to motivate the patient, not to impose specific recommendations on the optimization of PA. To solve this problem specialized professionals, such as clinical psychologists, may be involved in the exercises.

Factors that increase the patient's motivation to enhance PA:

- confidence in their own capacity for PA;
- getting pleasure from exercise;
- the realization that PA benefits outweigh all the arguments against;
- availability of social support (from family members, friends, etc.);
- active position of the doctor in increasing the patient's PA and his/her support.

The purpose of preventive counseling is to stratify patients by health groups, age, PA, fitness and motivation for PA.

Tasks implemented in the course of preventive counseling:

1. Primary assessment of patient's motivation to PA: in its absence — a brief conversation about the benefits of PA for a particular patient, taking into account his/her status.
2. For active patients in relation to PE — the primary assessment of individual PA level and, if necessary, the correction of a set of exercises in accordance with his/her health group, somatic status, age and degree of fitness.
3. Assessment of health status and identification of temporary contraindications for PA in training mode is carried out using various questionnaires (for example, IPAQ) filled in by the patient. Depending on the degree of motivation and the need to increase PA in the IPAQ questionnaire, there are three types of patients:
   a) with sedentary lifestyle, without intention to engage in PE in the next 6 months (according to IPAQ, item 1);
   b) planning or making attempts to increase PA (according to IPAQ, items 2–4);
   c) physically active persons (according to IPAQ, items 5–8).

The 6-minute walk test (recommended by ACSM, 2006 [28]) is a method of assessing the functional capabilities of patients, including in the presence of cardiac or bronchopulmonary diseases. This test is easy to use, it is necessary to have a 30-meter corridor. The distance that the patient can quickly walk on a flat, solid surface for 6 minutes is measured (Table 1). For healthy men, the average distance is 580 m, for healthy women — 500 m. Before using the test, it is necessary to conduct and analyze the resting ECG performed during the previous 6 months.

Test with squats (Aronov D. M., 1993 [29]). The maximum number of squats is performed at a convenient pace for the patient until fatigue develops. Then the stopwatch records the duration of the test and counts the number of squats, heart rate is measured initially and immediately after the termination of the test (standards are presented in Table 2).

The test with PE on cycle ergometer or treadmill is carried out in the form of a maximal (for group I of health) or submaximal (for groups II and III of health) exercise testing. Maximal exercise testing is used for examination of practically healthy, mostly young people who have an extremely low probability of having CHD, since it will be necessary to

Table 1. *Results of the 6-minute walk test, assessing physical exercises and prognosis in the prevention of cardiovascular complications (according to the recommendation of ACSM, 2006) **

Physical exercises levels	Number of meters	Prognosis for the prevention of cardiovascular complications
I	<300	Worst
II	300–374	Bad
III	375–450	Favorable
IV	>450	Very favorable

***Note:** the result should be compared with the proper value (in m), which is calculated by the formulas:
Men: (7.57 × height, cm) — (5.02 × age, years) — (1.76 — weight, kg) — 309 m
Women: (2.11 × height, cm) — (2.29 × weight, kg) — (5.78 × age, years) + 667 m

Table 2. *Standards of the test with squats depending on gender and age (Aronov D. M., 1993)*

Age, years	Number of squats per minute	
	Men	Women
29–39	34–42	32–38
40–49	31–41	29–35
50–59	27–35	26–34

Table 3. *Classification of weekly physical activity levels*

Levels of physical activity (power costs, MET min)	Physical activity of moderate intensity (min/week)	Utility for health	Comment
Absence	No physical activity above normal	No	Physical inactivity is a significant risk factor for cardiovascular disease
Low (<500)	<150 minutes in addition to normal	There are some benefits	Low level of physical activity is better than no physical activity
Average (500–1,000)	150–300 minutes to normal	Real benefit	This level of physical activity has additional health benefits
High (>1,000)	>300 minutes to normal	Added value	The limit level of physical activity, above which increase in additional health benefits does not occur is not defined

bring the heart rate of the patient to the maximum age-specific values or to complete exhaustion (the inability to further perform this exercise).

Exercise level criteria proposed by International Recommendations are presented in Table 3. These recommendations distinguish four categories of total weekly aerobic PA: lack of PA, low, medium and high levels of PA, determining the health benefit (risk).

Individualization of programs to increase patient's PA is achieved taking into account patient's group of health, his/her group of dispensary supervision (Order dated December 21, 2012 No. 1344n "On the approval of the procedure of carrying out dispensary supervision") and group of cardio-vascular risk.

- Group I of health — almost healthy, not in need of dispensary supervision.
- Group II of health — having RF of NCD, with high or very high total cardiovascular risk, are on dispensary supervision.
- Group III of health — have a disease and require dispensary supervision or specialized medical care, require additional examination.

Cardiovascular risk is determined by the SCORE system and corresponds to a 10-year risk of fatal CVD: low risk <1 %, medium risk 1 % — 4 %, high risk 5 % — 9 % and very high risk 10 % or more. Patients with CVD (after MI and CS, CHD, carotid atherosclerosis, chronic heart failure, etc.) belong to the group of very high cardiovascular risk. Such patients should be preceded by a medical examination before developing a plan to increase the intensity of PE.

It is mandatory to conduct medical examination for:

- persons over 40 years (smokers over 35 years),
- persons at high and very high cardiovascular risk,
- patients with established CVD (regardless of age and degree of their training),
- persons with a sedentary lifestyle, and therefore untrained [1].

Taking into account the specifics of the work of a general practitioner, in order to optimize the activities carried out by the general practitioner to increase PA in motivated patients, in accordance with the generally accepted methodology of preventive counseling, we propose a method of "Traffic Light": procedure of individual management of the patient for the organization of his/her physical activity regimen.

Traffic Light method: procedure of individual management of the patient for the organization of his/her physical activity regimen (Table 4)

1. Stages of consultation:

- To discuss the positive impact of PA on the improvement of individual health of the patient, improving his/her physical and psychological condition, the correction of RF, reducing the risk of NCD due to insufficient PA and to motivate him/her to include exercises in everyday life;
- To assess the state of health and to exclude contraindications for PA classes;

- To develop an individual program to improve PA, give recommendations on the choice of the appropriate type and level of PE, according to his/her age, fitness, health;
- To monitor the patient's compliance with PA recommendations, support his/her desire to achieve good results, to assess the changes of PA (result) and to make the necessary changes in the tactics of PA correction.

2. PA planning:

Planning takes the form of a discussion and is based on the following principles:

- The frequency of PA classes — at least 3–5 times a week, even daily;
- The duration of PA — 15–30 minutes, increasing to 45–60 minutes;
- The intensity of PE — 50–75 % of the maximal heart rate according to age (220-age) or individual threshold tolerance for patients with CVD and bronchopulmonary pathology;
- Type of exercise — dynamic.

3. Recommendations for PA optimization:

- Aerobic training should last at least 10 minutes (class IIA of recommendations, level A of evidence) [5].
- Aerobic PE should be spread evenly during the week — 4–5 days a week (class IIA of recommendations, level A of evidence) [5].
- People with sedentary lifestyles should undergo an adequate assessment of the possible risk and only then begin with mild PE programs (class I of recommendations, level A of evidence) [5].

General recommendations to increase daily PA are necessary for individuals with groups I and II of health. For persons of the third group, restrictions of routine and daily PA may be applied according to the underlying disease.

Patients belonging to any of the health groups, having a pathology of the musculoskeletal system, limiting PA, require an individual approach to the choice of the daily motor activity regimen.

With restrictions in health, for increase in PA, it is necessary to gradually increase the time of physical activity up to 150 minutes a week. This is possible due to the distribution of the total time for several classes per week, gradually increasing the duration of each class: for example, 30 minutes of PA of average intensity 5 times a week.

It is necessary to implement the basic principle of increasing PA: gradual increase in the duration of classes, their intensity and volume over several weeks.

It is desirable that the chosen exercises are available for performance and brought pleasure. Classes should be held 1.5–2 hours after meals and no later than 3 hours before bedtime.

If, for any reason, the training is interrupted, its resumption begins with a lower level, reaching the initial level gradually.

4. Control of PA classes:

PE intensity should not exceed 50–75 % of the maximum heart rate or individual tolerance to the performed exercise.

The optimal zones of the training regimen according to heart rate depending on the age are presented in Table 5. Patients are instructed on the importance of monitoring heart rate (pulse) during PA. For example, for a person aged 50 years (group II of health, without clinical signs of coronary heart disease) optimal training regimen can be provided with an exercise with the pulse from 100 to 125 beats per minute In the presence of CVD (group III of health), the level of permissible exercise is determined by the doctor individually, according to tests with PE.

Conclusion

Given the high efficacy and safety of PE in health promotion and prevention of NCD, it is desirable to carry out preventive counseling and make recommendations to optimize the level of PA depending on the age, degree of fitness, the health group of dispensary observation, the presence or absence of organic diseases for patients who are visiting a doctor for any reason.

Patients with high or very high risk of cardiovascular complications, having diseases of the cardiovascular, bronchopulmonary and other systems, recommendations for the optimization of PA should be preceded by thorough medical examination and, if necessary, consultation of specialists: cardiologist, pulmonologist, rehabilitation therapist and others, depending on the individual clinical pattern.

Table 4. *«Traffic Light» method: procedure of individual management of the patient for the organization of his/her physical activity regimen*

Risk of physical activity complications (including fatal)	**Health group, age**	**Initial physical activity (by express method of determination of physical condition)**	**Developer of physical activity regimen**	**Elimination of high risk of cardiovascular complications**	**Presence of a risk factor for chronic non-communicable diseases**	**Tactics (program) of physical activity [3]**	**Physical activity for the initiation of exercises for untrained patients or patients with sedentary lifestyle**	**Criteria for extent of exercises — submaximal age limit (220 — age of person)**	**Training mode**	**Physical activity monitoring**
"Green" risk zone	Group I 18–39 years 40–64 years Group I 40–64 years	Adequate physical activity (>75 points), you can use trackers and other gadgets	General practitioner (see General recommendations for improving daily physical activity) [2]	Test with squats 6-minute test	Absent or present at low risk of cardio-vascular complications	Gradual transition to the training mode, no restrictions on daily physical activity	Start physical activity with a dosed walk of 5–10 km/day and/or any kind of exercise, taking into account the cultural traditions of the family	Use circular exercises to bring heart rate up to 80 % of the norm in trained patients, up to 75 % of the norm in untrained patients	High (15–20 minutes) or moderate (30–40 minutes) intensity 3–5 times a week walking (untrained patients), swimming	Keeping a "Patient Diary". In the presence of poor tolerability of physical exercises (high heart rate and blood pressure at rest, disturbed sleep and appetite, health and mood, fatigue, weakness associated with physical activity, pain) — transition to the "Yellow zone" to review the tactics and for observation of the general practitioner[4]
"Yellow" risk zone	Group II 18–64 years	Average physical activity (46–74 points) ODA+ questionnaire	After consultation with GP (family doctor)	6-minute test and cycle ergometry (4-degree evaluation)	The presence of risk factors of chronic non-communicable diseases. With a low risk of cardiovascular complications, the patient moves to the "Green" zone, with a high risk — to the "Red" zone					
"Red" risk zone	Group I–III patients with chronic non-communicable diseases and/or patients over 65 years of age, very high cardiovascular risk according to SCORE	Low physical activity (<45 points) ODA+ questionnaire	GP, physical therapy instructor and/or rehabilitation specialist in medical institutions and at home	Cycle ergometry (4-degree evaluation	The presence of a risk factor for chronic non-communicable diseases, healthy patients >65 years of age, presence of chronic non-communicable diseases	Examination, initiation of physical activity in a differentiated individual mode of physical activity	Start with walking, switch to other types of individually selected exercises[4]	Taking into account the 6-minute test, bring the heart rate to 50–60 % of the norm, exercises in a medical or health institution according to the protocol of aerobic loads	Moderate individual intensity 2–5 times a week, duration and regularity are selected individually	

[1] Patients who have suffered a myocardial infarction, heart and heart vessels surgery, having stable angina or chronic heart failure, are recommended aerobic exercises of **moderate intensity** lasting **30 minutes 3 times or more per week** *(class I of recommendations, level A of evidence) [5].*

[2] Persons aged **18–64** are given physical activity / aerobic physical exercises of moderate intensity for **at least 150 minutes per week** (2 hours 30 minutes), *or* aerobic physical activity of high intensity for at least 75 minutes (1 hour 15 minutes) per week, *or* a similar combination of physical activity of moderate and high intensity (*class I of recommendations, level A of evidence). Main rule: 2 minutes of physical activity of moderate intensity are equal to 1 minute of physical activity of high intensity, for example, 30 minutes of physical activity of moderate intensity per week are similar to 15 minutes of physical activity of high intensity.*

[3] The initial level of physical exercises in untrained citizens should not increase the heart rate by more than 30 beats/min relative to rest, then the intensity of physical exercises increases until the optimal training heart rate is achieved.

[4] Adults (up to 65 years) should increase the moderate intensity load to 300 minutes (5 hours) per week *or* high intensity physical activity sessions to 150 minutes per week.

Note: Criteria for the effectiveness of physical exercises: heart rate and blood pressure at rest do not exceed safe standards, sleep, appetite, health and mood are improved, exercise tolerance increases, good performance of stress tests

Table 5. *Optimal zones of training regimen depending on age (heart rate equivalent to 60–75 % of MPC or maximum heart rate by age)*

Age, years	Heart rate, beats per minute	Age, years	Heart rate, beats per minute
20–29	115–145	60–69	95–115
30–39	110–140	70–80	88–108
40–49	105–130	80 and older	77–98
50–59	100–125		

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DOI: 10.20514/2226-6704-2019-9-4-280-289 UDC УДК 616.12-008.331.1-06:61624.-008.444-08

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BLOOD PRESSURE AND ARTERIAL STIFFNESS CHANGES DEPENDING ON THE DURATION OF CPAP NIGHT SESSIONS IN PATIENTS WITH SEVERE OBSTRUCTIVE SLEEP APNEA

Abstract

Numerous studies on the pathophysiological mechanisms of obstructive sleep apnea discover the relationship between obstructive sleep apnea and cardiovascular diseases, its contribution to the development of resistant hypertension and endothelial remodeling. Continuous Positive Airway Pressure (CPAP) is the only reasonable pathogenetic therapy in these patients. This treatment regimen implies the creation of a "pneumatic stent" with a given level of positive pressure on the inhalation and exhalation of the patient, allowing to stabilize the lumen of the upper respiratory tract and prevent the pharyngeal collapse. However, the effects and the required duration of CPAP night sessions to achieve the target values of blood pressure and restore arterial stiffness in patients with severe obstructive sleep apnea with resistant hypertension remain poorly understood. **Objective:** To study the dynamics of blood pressure, arterial stiffness and endothelial dysfunction in patients with severe obstructive sleep apnea with resistant hypertension, depending on the duration of auto-adjusting CPAP (A-Flex mode). **Methods:** The prospective single-center study enrolled 168 patients aged 35–75 y. o. with obstructive sleep apnea and resistant hypertension (139 males (82.7 %) and 29 females (17.3 %), 46.4 ± 9.0 y. o.) with apnea-hypopnea index >30 events/hour. The patients signed the informed consent and obtained adjusted antihypertensive treatment. The night polygraphy study was performed to calculate AHI, oxygen desaturation index, mean nocturnal saturation (SpO_2) according to the requirements of American Academy of Sleep Medicine. Endothelial function of blood vessels was assessed manually according to peripheral arterial tone. The reactive hyperemia index and augmentation index was calculated. Blood pressure was monitored by office measurement, daily monitoring of blood pressure, and by individual patient diaries. Optimal level of CPAP-treatment was adjusted on an outpatient basis. Apnea-hypopnea index, the level of air leakage, average pressure and compliance to CPAP-therapy were established in accordance with the international requirements. **Results:** In the group of patients, treated with night sessions of A-Flex >6 h/night, significant dynamics was observed by the 6th month of treatment. That is, a decrease in RHI by –1.33 (95 % CI [–2.25; –0.41]; P = 0.002), a decrease in AI by –12.4 % (95 % CI [–18.42; –6.38]; P = 0.001), a decrease in mean SBP (24 h) by –33.6 mm Hg (95 % CI [–44.1; –23.2]; P = 0.002) and decrease in mean DBP (24 h) by –20.2 mm Hg (95 % CI [–29.4; –11.1]; P = 0.001), with a decrease in SBP RMR by –22.4 mm Hg/h (95 % CI [–24.7; –20.1]; P = 0.002), and a decrease in DBP RMR by –17.4 mm Hg/h (95 % CI [–19.5; –15.3]; P = 0.003). The best target values were achieved by the 12th month of treatment: a decrease in RHI by –2.11 (95 % CI [–2.57; –1.65]; P = 0.001), a decrease in AI by -28.5 % (95 % CI [–37.06; –19.94]; P = 0.002), a decrease in mean SBP (24 h) by –39.7 mm Hg (95 % CI [–48.9; –30.5]; P = 0.001) and decrease in mean DBP (24 h) by –26.8 mm Hg (95 % CI [–36.1; –17.5]; P = 0.001), with a decrease in SBP RMR by –22.5 mm Hg/h (95 % CI [–23.6; –21.4]; P = 0.001), and a decrease DBP RMR by –19.4 mm Hg/h (95 % CI [–20.7;

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–18.1]; P = 0.002). **Conclusions:** In patients with severe obstructive sleep apnea and resistant hypertension only CPAP-therapy in the A-Flex mode >6 h/night allows to achieve target blood pressure, restores endothelial function and arterial stiffness, therefore reducing the risk of cardiovascular complications.

Key words: *obstructive sleep apnea, resistant hypertension, arterial stiffness, endothelial dysfunction, CPAP-therapy, A-Flex mode*

Conflict of interests

The authors declare no conflict of interests.

Source of financing

The authors state that no finding for the study has been received.

Article received on 05.05.2019

Accepted for publication on 08.07.2019

For citation: Gorbunova M. V., Babak S. L., Adasheva T. V. et al. BLOOD PRESSURE AND ARTERIAL STIFFNESS CHANGES DEPENDING ON THE DURATION OF CPAP NIGHT SESSIONS IN PATIENTS WITH SEVERE OBSTRUCTIVE SLEEP APNEA. The Russian Archives of Internal Medicine. 2019; 9(4): 280-289. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-280-289

AHI — apnea-hypopnea index, AI — augmentation index, CPAP — Continuous Positive Airway Pressure, ODI — oxygen desaturation index, PAT signal — peripheral arterial tone, RH — reactive hyperemia, RHI — reactive hyperemia index, PWA — pulse wave amplitude, SpO_2 — level of blood saturation, BP — blood pressure, BPV — blood pressure variability, DBP — diastolic blood pressure, OSA — obstructive sleep apnea, PG — polygraphic study, ResH — resistant hypertension, SBP — systolic blood pressure, ABPM — ambulatory blood pressure monitoring, SNS — sympathetic nervous system, RMR — rate of morning rise, CRM — Center of Respiratory Medicine, HR — heart rate

Introduction

Obstructive sleep apnea (OSA) is associated with periodic development of upper respiratory tract collapses during nighttime. As a result of respiratory arrests, alveolar ventilation changes, and acute hypoxemia episodes with sharp increase in breathing efforts and substantial change in intrathoracic negative pressure occur. Large-scale prospective clinical studies proved the relationship between OSA and increased risk of cardiovascular diseases, including resistant hypertension (ResH) [1, 2]. Intermittent hypoxemia (cyclic desaturation with fast reoxygenation) occurring at the time of sleep apnea contributes to the formation of reactive oxygen intermediates, activates oxidative stress, and initiates endothelial vascular injury cascade [3]. Chronic inflammation results in vascular injury with further remodeling of blood vessels. Currently, arterial stiffness is recognized as a criterion of vascular ageing and a risk factor of cardiovascular events [4, 5]. Moreover, activated sympathetic nervous system (SNS), and amplified peripheral and central chemoreflexes cause a steady increase of blood pressure (BP) [6]. By removing pharyngeal collapses, Continuous Positive Airway Pressure (CPAP) therapy stops anoxemia episodes, reduces sympathetic tone and negative intrathoracic pressure fluctuations [7]. However, the duration of ventilatory care in patients with ResH+OSA is poorly understood, which was the reason for conducting this study.

Materials and methods

Study design

Our single-center prospective study enrolled 168 patients with hypertension and metabolic disorders (139 males, or 82.7 %, and 29 females, or 17.3 %), aged 46.4 ± 9.0 years, who had severe OSA (apnea-hypopnea index (AHI) >30 events/hour) and who had signed an informed consent (Figure 1).

All the patients underwent physical and complete medical examination with an additional focus on history, symptoms and markers of sleep respiratory disorders (STOP BANG Questionnaire) [8]. They were interviewed for how long they had been gaining weight and when it started, number of attempts to lose weight, administration of weight management medications and/or dietary supplements,

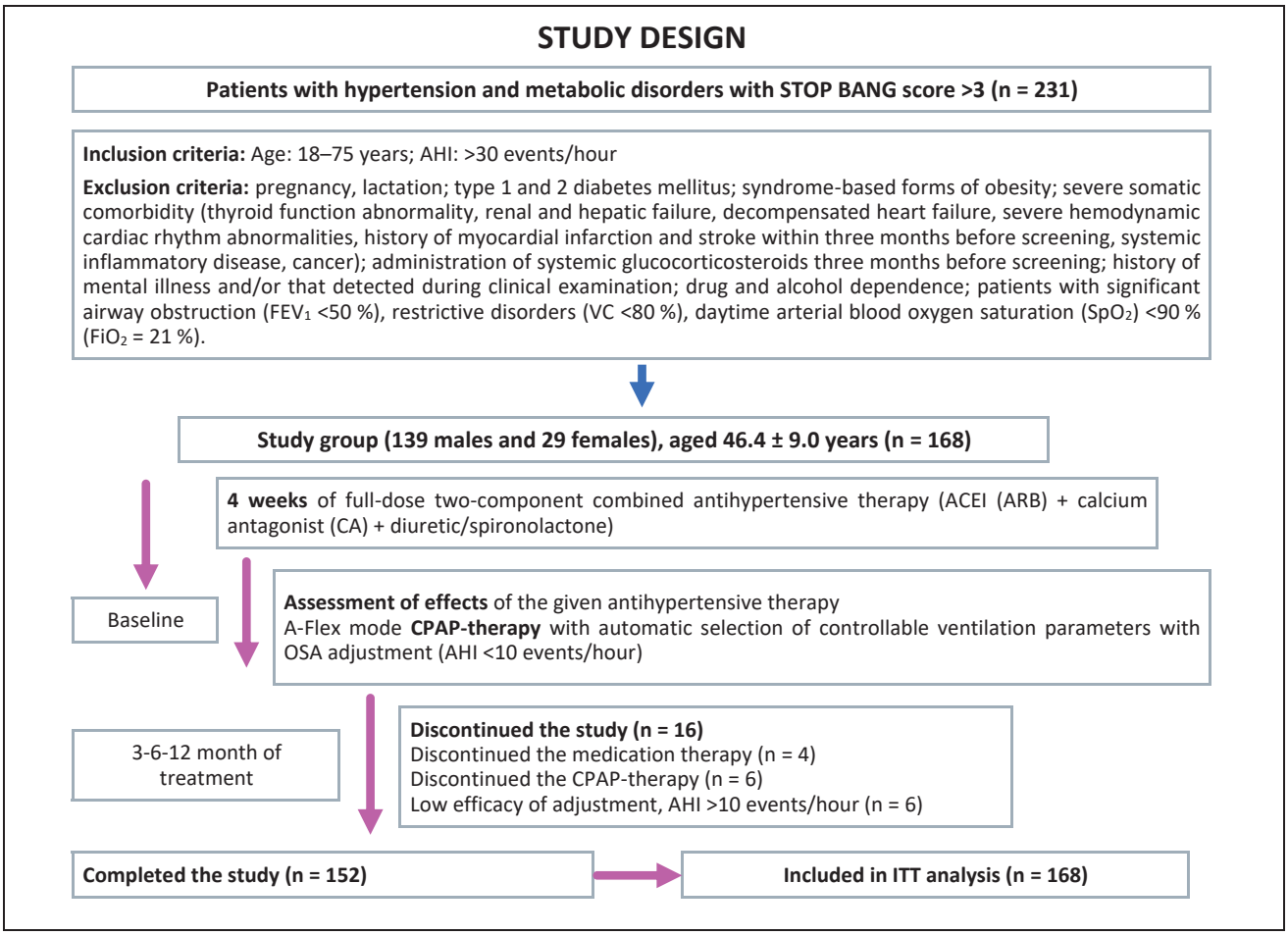

Figure 1. *Scheme of the study design. Explanations are given in the text*

dietary habits and daily dietary calories, physical activity. The exclusion criteria were: pregnancy, lactation; type 1 and 2 diabetes mellitus; syndrome-based forms of obesity; severe somatic comorbidity (thyroid function abnormality, renal and hepatic failure, decompensated heart failure, severe hemodynamic cardiac rhythm abnormalities, history of myocardial infarction and stroke within three months before screening, systemic inflammatory disease, cancer); administration of systemic glucocorticosteroids three months before screening; history of mental illness and/or that detected during clinical examination; drug and alcohol dependence; patients with significant airway obstruction (FEV_1 <50 %), restrictive disorders (VC <80 %), daytime arterial blood oxygen saturation (SpO_2) <90 % (FiO_2 = 21 %).

All patients received the full-dose two-component combination antihypertensive therapy (ACE inhibitors (ARB) + calcium antagonist (CA) + diuretic/spironolactone) [9] for 4 weeks with the assessment of effects of ResH medication adjustment in patients with OSA before respiratory support. In subsequent 3–6–12 months, all patients with OSA+ResH received auto-adjusting CPAP-therapy (A-Flex mode) in accordance with the recommendations of the American Academy of Sleep Medicine (AASM) [10] to achieve the optimal OSA adjustment with AHI <10 events/hour with preservation of the selected antihypertensive medication therapy.

Ethical standards

The study was conducted in the Department of Phthisiology and Pulmonology of the General Medicine Faculty at the A. I. Evdokimov Moscow State University of Medicine and Dentistry based

on the Center of Respiratory Medicine and the Hospital of Centrosoyuz of the Russian Federation (39 Losinoostrovskaya street, bldg. 2, Moscow, 107150, Russia). The study was approved by the Inter-University Ethics Committee of the A. I. Evdokimov Moscow State University of Medicine and Dentistry.

Polygraphic study

All the patients underwent a night polygraphic study (PG) as per the standardized protocol for cardiovascular monitoring of obstructive sleep apnea in accordance with the American Academy of Sleep Medicine (AASM) regulations and recommendations [11]. SOMNOcheck micro CARDIO (Lowenstein Medical (Weinmann), Germany) with SOMNOlab 2.19 (Lowenstein Medical (Weinmann), Germany) software was used. The study was started at 11.00 p. m. and completed at 7.30 a. m., with registration of the main polygraphic respiratory parameters: 1) mouth-nose airflow and snoring; 2) breathing efforts; 3) recording of SpO_2 and heart rate (HR) by pulse oxymetry. The polygraphy findings were processed manually by the qualified personnel of the CRM. Apnea was identified as reduction in the airflow signal by >80 % while maintaining the breathing effort for >10 seconds. Hypopnea was identified as reduction in the airflow signal by >30 % while maintaining the breathing effort for >10 seconds and subsequent desaturation by >4 %. Severity of OSA was determined by the apnea-hypopnea index (AHI) defined as the total number of obstructive apnea and hypopnea per 1 recording hour. Occurrence of 5< AHI <15 events/hour was assessed as mild OSA; 15< AHI <30 events/hour — as moderate OSA; AHI >30 events/hour — as severe OSA. The assessment included the nocturnal desaturation level by ODI, i. e., the number of drops of SpO_2 >4 %, as well as mean and minimum nocturnal saturation (SpO_2), respectively.

Endothelial function assessment

Vascular endothelial function was assessed by the quality of peripheral arterial tone (PAT signal) measured manually using two modified plethysmographic biosensors placed on forefingers of both hands [12]. Pulse wave amplitude (PWA) was estimated before and during reactive hyperemia (RH) by peripheral arterial tonometry (Endo-PAT2000, Itamar Medical Ltd., Israel). Ischemic stimulus was induced by cuff occlusion (shoulder cuff inflation up to systolic pressure of >200 mm Hg for 5 min), and the reactive hyperemia index (RHI) was calculated as a ratio of mean PWA for a period of 1 minute after cuff deflation to the baseline pre-occlusion PWA. We estimated the augmentation index (AI) defined as a ratio of the shock wave arising from the increase of aortic pressure to the systolic reflected wave [13]. All tests of RHI and AI were performed under standardized conditions (time, room, temperature).

Ambulatory blood pressure monitoring (ABPM) was performed using the BPLab 24-hour recording outpatient device, model MnSDP-2 (Petr Telegin, Russia). BP was recorded every 15 minutes during daytime and every 30 minutes at night. Sleep and wake intervals were determined individually, based on the patients' diaries. Examining 24-hour BP profile, we analyzed arithmetic means of systolic blood pressure (SBP), diastolic blood pressure (DBP) during day- and nighttime, as well as over 24 hours. To interpret the daily BP rhythm, the degree of nocturnal pressure reduction was used by calculating the daily index (DI, %) based on BP daily (BP_d) and nocturnal average values (BP_n), as calculated by the formula: $DI = 100\ \% \times (BP_d - BP_n)/BPd$. Based on the DI data, the following types of daily BP profile were determined: patients with normal nocturnal BP reduction (dippers): 10< DI <20 %; patients with insufficient nocturnal BP reduction (non-dippers): 0< DI <10 %; patients with higher nocturnal BP reduction (over-dippers): DI over 20 %; patients with steady increase in nocturnal BP (night-peakers): DI less than 0 %. Blood pressure variability (BPV) was assessed as a standard deviation of individual BP values from the daily and/or nocturnal mean value. Variability for SBP during day- and nighttime should not exceed 15 mm Hg, for DBP — 14 mm Hg during daytime and 12 mm Hg during nighttime. High BPV was registered when any of the four mentioned parameters deviated. The rate of morning BP rise was calculated by the ratio of the BP rise value to its time [14].

Assessment of compliance with CPAP-therapy

The optimum treatment level of CPAP-therapy was adjusted on an outpatient basis using pressure auto-select devices (PR System One REMstar Auto CPAP Machine with A-Flex (Philips Respironics, USA)) for 7 days following the diagnostic testing. To assess the compliance of patients with OSA on Month 3–6–12 of CPAP-therapy, we used Encore Pro v.2.14 original compliance analysis program (Philips Respironics, USA). The primary analyzed parameters included: 1) the mean time of CPAP-therapy for all days of usage (AU) (h/night) — an index that reflects the repeatability of CPAP-therapy in case of outpatient usage; 2) the average treatment pressure of CPAP-therapy (CMP) (mbar) — an index that reflects the treatment pressure of CPAP-therapy; 3) the average correctional apnea-hypopnea index during CPAP-therapy (AHI_{CPAP}) (events/hour) — an index that reflects the efficacy of CPAP-therapy. Based on the level of usage of nocturnal auto-adjusting CPAP-therapy (A-Flex mode), the patients were divided into the following groups: 1) <4 h/night — low compliant patients with OSA (group A); 2) 4 to 6 h/night — medium compliant patients with OSA (group B); 3) >6 h/night — high compliant patients with OSA (group C) [15].

Statistical analysis

Mathematical processing of the results was performed using the SPSS 12.0 software package (SPSS Inc., USA). Before the statistical analysis, the pattern of distribution of individual indicators was assessed according to the Kolmogorov — Smirnov test. The analysis was performed using single factor methods of parametric and non-parametric statistics. The Bonferroni method was applied for pairwise comparisons. If the quantitative attributes were distributed abnormally, the significance of group differences was examined using the Mann — Whitney U-test. Quantitative data was expressed as mean (M) and standard deviation (SD) (M±SD). During the final assessment of the findings, we performed the intention-to-treat analysis (ITT analysis) [16]. Moreover, methods of multivariate statistics should be used to reveal "hidden" factors affecting the result. The χ^2 test, the so-called likelihood ratio, was used to compare qualitative data; when no assumptions were made, the Fisher's exact test was applied. Differences in the tested parameters were considered significant at $p < 0.05$. When $0.05 < p < 0.1$, the existence of a statistical trend was estimated [17].

Results

Characteristics of the group with OSA+ResH (n = 168) after 4 weeks of the full-dose two-component combined antihypertensive therapy (ACE inhibitor (ARB) + calcium antagonist (CA) + diuretic/spironolactone) are presented in Table 1.

Of the 168 enrolled patients, a total of 152 (90.5 %) patients made every visit and were included in the standard analysis. Sixteen patients (9.5 %) discontinued their participation in the study by Month 12 due to: 1) self-determined termination of the medication therapy (n = 4); 2) self-determined termination of CPAP-therapy (n = 6); 3) low efficacy of A-Flex on Month 3 of observation with the preservation of AHI >10 events/hour (n = 6). All the patients were included in the subsequent ITT analysis.

It should be noted that, despite the full-dose combination medication therapy, patients with severe OSA+ResH had high BMI, severe nocturnal hypoxemia, and increased office SBP/DBP. They had low baseline RHI (endothelial function) and high baseline AI (arterial stiffness). The analysis of ABPM revealed a moderate increase in SBP/DBP with the expressed daily profile disturbance. The majority of patients (n = 115; 68.4 %) were assessed as non-dippers. They had increased blood pressure variability during day-/nighttime, as well as high rate of morning SBP/DBP rise.

Intention-to-treat (ITT) analysis of SBP/DBP, arterial stiffness and endothelial function

The mean medical pressure of CPAP-therapy (CMP) for all patients in the group was 14.40 ± 2.50 mbar with the apnea-hypopnea index (AHI_{CPAP}) adjusted to 6.90 ± 2.12 events/hour, which demonstrated that the OSA control target was achieved and the risk of probable fatal and non-fatal cardiovascular events was entirely eliminated [15].

Table 1. *Baseline characteristics of patients with hypertension+OSA (n = 168)*

Test parameter	BASELINE (n = 168)
Age (years)	46.40 ± 9.03
Gender (male/female)	139/29
Body mass index (BMI) (kg/m^2)	37.40 ± 3.60
Neck circumference (cm)	44.30 ± 3.81
Waist circumference (cm) males females	 121.40 ± 9.20 110.3 ± 11.60
Smokers (n, (%))	18 (10.7)
Ex-smokers (n, (%))	125 (74.4)
Never-smokers (n, (%))	25 (14.8)
Nocturnal polygraphic study (PG) parameters	
Apnea-hypopnea index (AHI) (events/hour)	49.8 ± 6.90
Oxygen desaturation index (ODI) (events/hour)	46.5 ± 4.70
Time required for saturation less than 90 % (TSat_90) (% of the total sleep time)	27.8 ± 3.40
Mean nocturnal saturation (Sat mean) (%)	83.1 ± 2.30
Minimum nocturnal saturation (Sat min) (%)	70.5 ± 4.20
Minimum nocturnal HR (beats/min)	43.1 ± 4.10
Maximum nocturnal HR (beats/min)	113.2 ± 7.30
Office SBP/DBP, reactive hyperemia index (RHI), augmentation index (AI)	
Hypertension duration, years	9.50 ± 2.90
Office SBP, mm Hg	163.20 ± 17.3
Office DBP, mm Hg	99.50 ± 7.11
Reactive hyperemia index (RHI) (reference <1.67)	3.30 ± 0.82
Augmentation index (AI) (%) (reference: 18.43–39.97 %)	47.10 ± 4.4
SBP/DBP ambulatory monitoring (ABPM) parameters	
Mean SBP (24 hours), mm Hg	151.1 ± 12.2
Mean DBP (24 hours), mm Hg	92.3 ± 10.1
Mean SBP (day), mm Hg	154.3 ± 13.4
Mean DBP (day), mm Hg	88.4 ± 8.3
Mean SBP (night), mm Hg	150.4 ± 12.1
Mean DBP (night), mm Hg	86.5 ± 7.4
SBP variability (day), mm Hg	22.4 ± 6.3
DBP variability (day), mm Hg	18.1 ± 2.4
SBP variability (night), mm Hg	25.3 ± 5.2
DBP variability (night), mm Hg	18.9 ± 4.6
dippers, (n, %)	7 (4.2)
non-dippers, (n, %)	115 (68.4)
night peakers, (n, %)	46 (27.4)
over-dippers, (n, %)	0 (0)
SBP RMR, mm Hg/h	29.6 ± 3.1
DBP RMR, mm Hg/h	23.4 ± 4.2

Table 2. *Changes in SBP/DBP, arterial stiffness and endothelial function parameters (n = 168)*

Test parameter	Baseline (without CPAP)	Month 3 CPAP	Month 6 CPAP	Month 12 CPAP
Reactive hyperemia index (RHI)	3.30 ± 0.82	3.10 ± 0.85	2.89 ± 0.92*	1.65 ± 0.46**
Augmentation index (AI) (%)	47.10 ± 4.4	45.20 ± 5.60	40.70 ± 6.02*	27.15 ± 8.56**
Mean SBP (24 hours), mm Hg	151.1 ± 12.2	133.2 ± 11.3*	124.2 ± 10.4**	119.4 ± 9.2**
Mean DBP (24 hours), mm Hg	92.3 ± 10.1	83.2 ± 10.1*	76.3 ± 9.2**	71.4 ± 9.3**
Mean SBP (day), mm Hg	154.3 ± 13.4	136.7 ± 11.4*	126.3 ± 10.3**	121.2 ± 9.5**
Mean DBP (day), mm Hg	88.4 ± 8.3	82.0 ± 8.1*	75.1 ± 7.3**	71.3 ± 7.3**
Mean SBP (night), mm Hg	150.4 ± 12.1	130.1 ± 11.7*	120.4 ± 9.1**	115.3 ± 9.2**
Mean DBP (night), mm Hg	86.5 ± 7.4	81.4 ± 7.2*	72.2 ± 6.1**	70.5 ± 5.4**
SBP variability (day), mm Hg	22.4 ± 6.3	15.4 ± 3.7*	11.3 ± 3.3**	10.5 ± 2.2**
DBP variability (day), mm Hg	18.1 ± 2.4	13.2 ± 2.5*	10.5 ± 3.4**	9.6 ± 2.8**
SBP variability (night), mm Hg	25.3 ± 5.2	15.7 ± 3.2*	10.5 ± 3.1**	10.1 ± 2.3**
DBP variability (night), mm Hg	18.9 ± 4.6	13.7 ± 3.9*	9.6 ± 2.3**	8.8 ± 3.1**
SBP RMR, mm Hg	29.6 ± 3.1	14.6 ± 3.9*	9.5 ± 2.3**	8.2 ± 1.1**
DBP RMR, mm Hg	23.4 ± 4.2	13.8 ± 2.7*	8.1 ± 2.1**	5.3 ± 1.3**

Note: RMR — rate of morning rise;
*ρ <0.05 against the baseline values (without CPAP), **ρ <0.01 against the baseline values (without CPAP)

We performed the intention-to-treat (ITT) analysis of SBP/DBP, RHI, AI adjusted for age, gender, BMI, conducted antihypertensive therapy, depending on the duration of daily night A-Flex sessions (CPAP-therapy). Changes in average values for the group (n = 168) of primary parameters on Months 3, 6, and 12 of the therapy are presented in Table 2.

In general, significant positive changes in SBP/DBP, RHI and AI against the background of CPAP-therapy occurred as early as Month 3. However, we found significant differences in the rate of achievement of the target test parameters depending on the duration of night sessions of A-Flex therapy. For example, patients who received A-Flex <4 h/night had the least changes (Figures 2, 3, 4).

Significant positive changes in the group of patients who received A-Flex >6 h/night occurred by Month 6: RHI decreased by –1.33 (95 % CI: –2.25 to –0.41; P = 0.002), AI decreased by –12.4 % (95 % CI: –18.42 to –6.38; P = 0.001), mean SBP (24-hour) decreased by –33.6 mm Hg (95 % CI: –44.1 to –23.2; P = 0.002) and mean DBP (24-hour) — by –20.2 mm Hg (95 % CI: –29.4 to –11.1; P = 0.001), with decrease of SBP RMR by –22.4 mm Hg/hour (95 % CI: –24.7 to –20.1; P = 0.002) and DBP RMR — by –17.4 mm Hg/hour (95 % CI: –19.5 to –15.3; P = 0.003). The best target values were achieved only in the group of patients who received A-Flex >6 h/night on Month 12 of A-Flex therapy: RHI decreased by –2.11 (95 % CI: –2.57 to –1.65; P = 0.001), AI decreased by –28.5 % (95 % CI: –37.06 to –19.94; P = 0.002), mean SBP (24-hour) decreased by –39.7 mm Hg (95 % CI: –48.9 to –30.5; P = 0.001) and mean DBP (24-hour) — by –26.8 mm Hg (95 % CI: –36.1 to –17.5; P = 0.001), with decrease of SBP RMR by –22.5 mm Hg/hour (95 % CI: –23.6 to –21.4; P = 0.001) and DBP RMR — by –19.4 mm Hg/hour (95 % CI: –20.7 to –18.1; P = 0.002).

Discussion

Obstructive sleep apnea is a heterogeneous disease with a complex development mechanism and high risks of cardiovascular complications [2]. In our study, we tried to analyze patients with hypertension and severe OSA who had the maximum risks of fatal events. Currently, CPAP-therapy is recognized

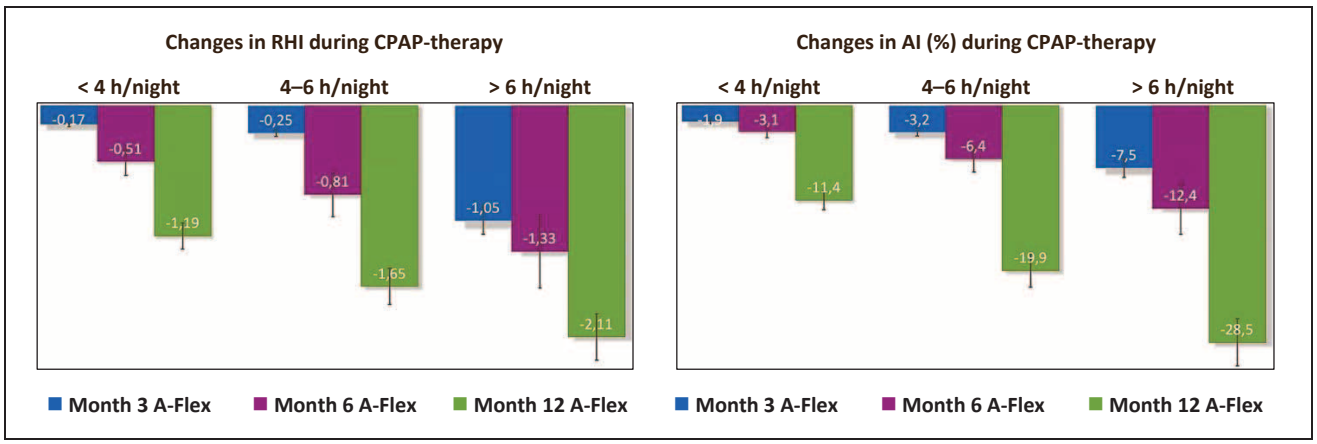

Figure 2. *Changes in RHI and AI depending on the duration of A-FLEX night sessions on Months 3–6–12. Explanations are given in the text*

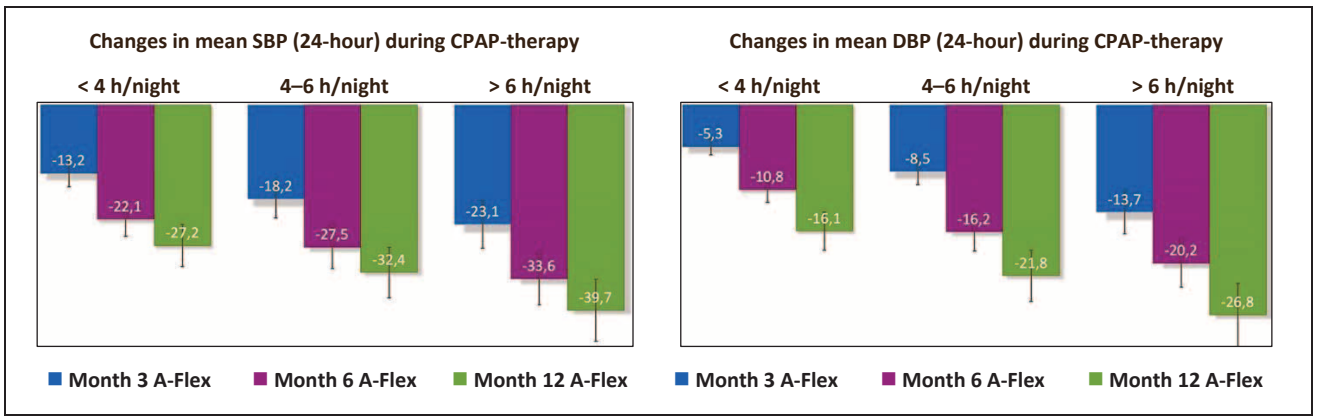

Figure 3. *Changes in mean SBP/DBP depending on the duration of A-FLEX night sessions on Months 3–6–12. Explanations are given in the text*

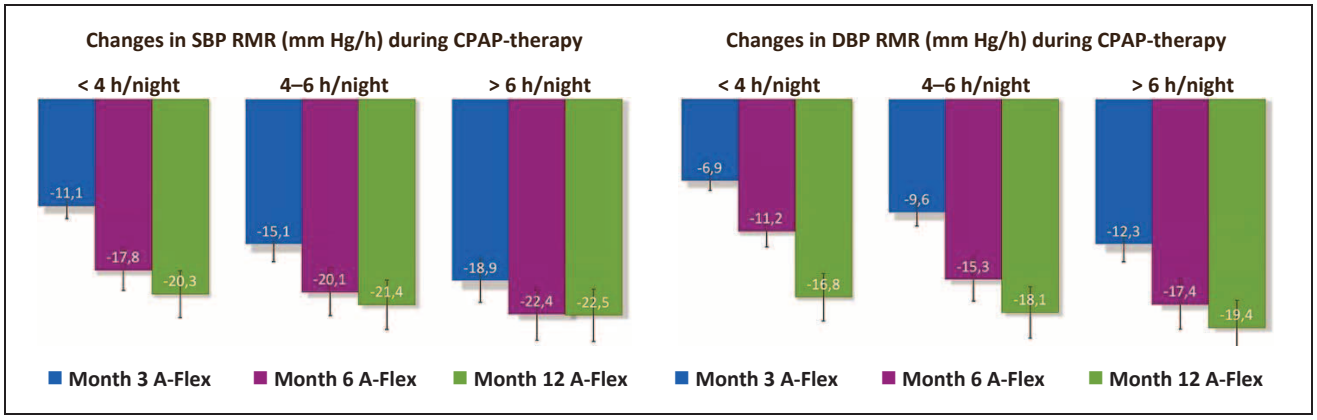

Figure 4. *Changes in rates of morning SBP/DBP rise depending on the duration of A-FLEX night sessions on Months 3–6–12. Explanations are given in the text*

as the only reasonable pathogenetic therapy for this disease [10]. However, various modes of CPAP and the required duration of night sessions are still understudied, especially for comorbid patients with OSA+ResH [18].

Despite the simple design, no blinding, placebo control and randomization of patients, we achieved the minimum effect on the endpoint through formation of the study group and use of the intention-to-treat (ITT) analysis [16].

Our findings are fully consistent with a number of studies on the impact of CPAP-therapy on the normalization of the endothelial function, arterial stiffness and blood pressure in patients with OSA [18, 19]. However, we first established special features of A-Flex night sessions in patients with severe OSA+ResH, when its duration of >6 h/night made it possible to achieve the target SBP/DBP, RHI and AI on Month 6. It should be noted that the low baseline efficacy of the full-dose combination antihypertensive therapy in patients with OSA is directly related to sleep fragmentation, nocturnal hypoxemia, nocturnal sympathetic activity [3]. This hypothesis is supported by our study when only combination full-dose drug and non-drug CPAP-therapy conducted for over 6 h/night significantly restores SBP/DBP, endothelial function and vascular stiffness to the target values, even in patients with severe OSA+ResH.

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DOI: 10.20514/2226-6704-2019-9-4-290-295 UDC616.12-008.331.1:616.124.2-036-08

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THE LEFT VENTRICLE DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTENSION UNDER THE USE OF DIFFERENT DRUG GROUPS

Abstract

The objective: To assess the prevalence of diastolic dysfunction in patients with hypertension and preserved left ventricular ejection fraction under pharmacological correction (monotherapy) with angiotensin converting enzyme inhibitors, angiotensin receptor blockers and β-blockers. **Materials and methods**: 82 patients (58 women and 24 men) with stage 2 hypertension were examined. The diastolic function was assessed via echocardiography in accordance with the European Association of Cardiovascular Imaging guidelines (2017). Echocardiography was performed before the onset of the treatment and 6 months after its onset. The treatment onset was considered to start after a 2-week period of elimination of previously used pharmacological substance and 2 weeks of assessing tolerability, dose and regimen adjustment. **Results**: For all selected drugs, target values of blood pressure were achieved, and no adverse effects were identified. The average values of the left atrial volume index before and after the treatment course did not show significant differences. In the majority of the examined patients, this parameter did not exceed the threshold value of 34 ml/m^2. Values exceeding the specified threshold were observed in Group 1 in 4 patients, in Group 2 in 3 patients and in Group 3 in 8 patients. According to the tissue Doppler ultrasound results on the velocity of myocardial motion at the early diastolic filling of the left ventricle, which was measured at the level of the lateral segments of mitral valve and the interventricular septum, positive, but unreliable, changes were observed in the groups of bisoprolol and valsartan, and no changes — in the group of perindopril. According to the traditional criteria, diastolic dysfunction was observed in 80 % of patients, while according to the criteria of the European Association of Cardiovascular Imaging (2017) — in 21 % of patients. **Conclusion**: The same efficacy of all three drugs is observed in terms of achieving target blood pressure values. The most pronounced effect on the morphometric parameters of the left atrium and intracardiac hemodynamics is shown in the groups of bisoprolol and valsartan.

Key words: *hypertension, diastolic dysfunction, echocardiography, tissue Doppler ultrasound, valsartan, perindopril, bisoprolol*

Conflict of interests

The authors declare no conflict of interests.

Source of financing

The authors states that no finding for the study has been received.

Article received on 24.04.2019

Accepted for publication on 08.07.2019

For citation: Budnevskiy A. V., Ovsyannikov E. S., Kulikova L. E. THE LEFT VENTRICLE DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTENSION UNDER THE USE OF DIFFERENT DRUG GROUPS. The Russian Archives of Internal Medicine. 2019; 9(4): 290-295. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-290-295

BP — blood pressure; ARBs — angiotensin receptor blockers; EH — essential hypertension; DBP — diastolic blood pressure; DD — diastolic dysfunction; ACEI — angiotensin converting enzyme inhibitors; LV — left ventricle; LA — left

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atrium; SBP — systolic blood pressure; HF — heart failure; CVD — cardiovascular diseases; LVEF — left ventricular ejection fraction; ECHO-CG — echocardiography

Introduction

Hypertension is one of the biggest problems facing modern medicine. This is due to the polyetiology of increased blood pressure (BP), discovering multifaceted capabilities for therapeutic interventions in this condition, depending on its causes and concomitant diseases, as well as on the formation of pathophysiological vicious circles contributing to the deterioration of the patient's condition [1]. Multiple target organ damage is an additional factor, which exacerbates the progression of hypertensive conditions and is important for mortality rate development. Vascular accidents appearing against the background of elevated BP are known to be among the top three causes of death worldwide [2–4].

Changes in systemic and intracardiac hemodynamics in various hypertensive conditions are widely known. Currently, there is a wide range of diagnostic methods to identify said abnormalities on time. These include noninvasive assessment of the heart using echocardiography (ECHO-CG) [1, 5, 6]. This method allows to study morphometric parameters (wall thickness, sizes of the cardiac chambers and the main vessels), state of heart valves, and to assess intracardiac flows using Doppler methods. Investigations of changes in myocardial thickness, their temporal characteristics, reflecting the dynamics of heart muscle contraction and relaxation, are traditionally used to study the mechanics of heart contraction. Today, said possibilities are supplemented with widespread introduction of the tissue Doppler ultrasound, which significantly expanded the diagnostic capabilities of the method, in particular, relating to assessment of the diastolic state of myocardium [5–8].

Quite often, cardiac damage in hypertension is accompanied by the development of left ventricle (LV) diastolic dysfunction (DD) [8]. This condition includes changes in diastolic filling of the ventricle, accompanied by a decrease in ventricular distensibility and impairment in its relaxation. DD is of particular interest as a specific point connecting hypertension and the development of heart failure (HF), especially in patients with normal parameters of the LV systolic function, namely with normal or slightly reduced ejection fraction (EF). Numerous studies have shown that DD is very common among patients with cardiac diseases, and it can be both isolated and combined with systolic function impairment. Of particular interest is that the occurrence of symptomatic HF and sudden cardiac death is a specific consequence of DD, even with intact EF [1, 2, 8].

Also, elevated BP contributes greatly to the causes of mortality from cardiovascular diseases (CVD) due to the fact that it leads to system, structural and functional remodeling involving multiple body organs and systems: changes in vessel wall stiffness, progressing nephropathy, and cardiac changes including diastolic and systolic dysfunction, as well as LV myocardial hypertrophy. According to the latest research, heart failure with normal EF is a socially significant health problem, because more than half of patients with early HF are known to have no changes in EF. Moreover, in recent decades there has been a tendency towards an increase in frequency of this condition with simultaneous increase in mortality from it [1, 2, 9].

Investigation of the incidence and manifestations of HF with intact EF is even more important due to the fact that to date, approaches to its pharmacological correction are underdeveloped, despite the common use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in decreased EF, which increase survival in patients with heart failure [1, 6, 10–13]. The above data indicate the social significance of studying diagnostic methods for HF with an intact EF and approaches to its drug correction in the presence of a combination of hypertension and LV diastolic dysfunction.

The aim of the study was to assess the frequency of diastolic dysfunction in patients with hypertension and an intact EF under conditions of pharmacological correction (monotherapy) with ACEI, ARB, and β-blockers.

Study objectives:

- assess the frequency of DD in patients with essential hypertension (EH), 2nd degree, 2nd and 3rd stage (according to the Russian classification), based on echocardiography data
- identify the most common DD markers
- assess changes in intracardiac hemodynamics parameters with pharmacological correction by antihypertensive agents of various groups

Materials and methods

The study had an open, non-randomized, prospective design.

Inclusion criteria: voluntary informed consent of the patient to participate in the study, diagnosis of 2nd–3rd stage and 2nd degree EH, blood glucose below 5.5 mmol/L, waist circumference less than 102 cm in men and 88 cm in women, sinus rhythm on ECG, type 1 DD.

Exclusion criteria: thyroid disease, chronic liver disease, secondary hypertension, history of use of 3 or more antihypertensive agents, exceeding the threshold values of lipid spectrum parameters, acquired or congenital cardiac abnormalities.

The clinical group consisted of 82 patients, of whom 58 were women and 24 were men, who underwent examination and treatment at the medical center "MedExpert". The mean age of the patients was 58.6 ± 7.4 years. The patients were divided into three groups. Bisoprolol as monotherapy was used in the first group, which consisted of 25 patients. The second group included 23 patients who were treated with perindopril. The third group consisted of 32 patients who were treated with valsartan. The distribution of patients by age is shown in Figure 1.

The patient examination included examination by a general practitioner and a cardiologist, complete blood count, urinalysis, biochemical blood test — glucose, lipid spectrum, urea, creatinine, 24-hour ECG monitoring, and chest X-ray. All patients underwent an echocardiographic study (ECHO-CG) immediately after prescription of drug therapy and 6 months from its start. ECHO-CG was performed on Logiq S8, manufactured by General Electric (USA). The study was conducted by the standard method with morphometric assessment of cardiac chamber sizes, thickness of the left and right ventricle myocardium, diameters of the aorta and pulmonary trunk at the level of the valve ring, EF calculation (in case of LV cavity remodeling, by Simpson and Teichholz method), and assessment of local myocardial contractility. The left atrium (LA) volume and LA volume index were calculated from apical four- and two-chamber views. The study of

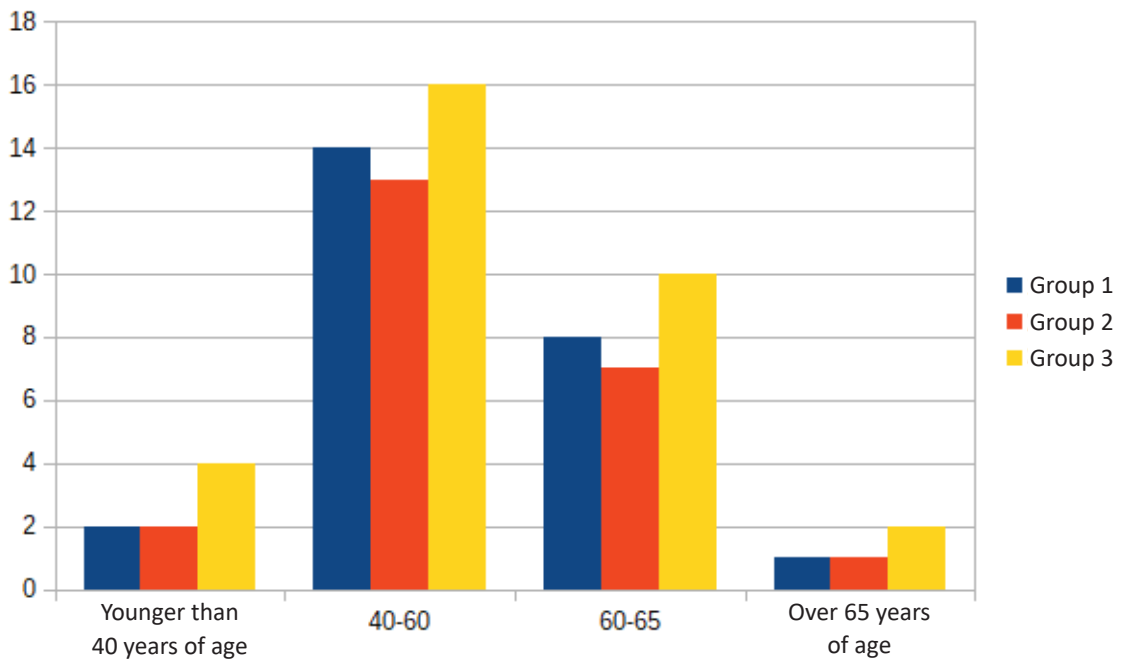

Figure 1. *The distribution of patients in the study groups by age*

DD parameters included the use of the tissue Doppler ultrasound with detection of LV myocardial velocity parameters at the level of the valve ring in septal and lateral parts with evaluation of e' lateral and septal, e'_{lat} and e'_{sept}. The intracardiac hemodynamics parameters were assessed using continuous-wave pulsed Doppler ultrasound, and values of early diastolic filling of the ventricles (E) and ventricular filling in atrial systole (A) were detected to assess blood flow through atrioventricular valves. In case of regurgitant flows, their velocity parameters were detected using continuous-wave Doppler ultrasound. Blood flow at the level of pulmonary veins ostia was evaluated by pulsed Doppler ultrasound in apical four-chamber view. Said additions to the standard protocol comply with the European Association of Cardiovascular Imaging guidelines of 2017 [13].

The results obtained were entered into a Microsoft Excel spreadsheet and processed using Statistica 10.0 software (Dell). The mean sample values were analyzed and compared using nonparametric Wilcoxon-Mann-Whitney tests and Friedman test. The top 2.5 % part of Friedman's F distribution was used as test statistics. Numerical values in the article are presented by median and interquartile range, as well as mean ± standard deviation.

After a 2-week period of elimination of the pharmacological substance of previously used agents, the compared drugs were prescribed for 14 days to assess tolerability, to select the dose and dosage regimen. Dose selection was performed by titration method starting with minimum doses. Bisoprolol, starting from 1.25 mg, with a gradual increase to achieve clinical effect presented as HR decrease to the selected threshold values and BP values near to the target ones (below 140 and 90 mm Hg). Valsartan, starting from 20 mg, the maximum dose did not exceed 80 mg per day (once daily). Perindopril was prescribed at the initial dose of 2 mg until achieving said target HR and BP values (once daily). During the study, no cases of adverse effects of said treatment were observed.

Results and discussion

Significant decrease of BP measured at brachial artery was observed in all patients when using all of the selected agents. The values for BP parameters are provided in Table 1.

When assessing the efficacy of the provided therapy 6 months after its start, BP was shown to have decreased to the target values in 23 of 25 patients (or 92 %) in the first group, in 21 of 23 patients (91.3 %) in the second group, and in 30 of 32 patients (93.8 %) in the third group. Thus, sufficiently high efficiency was shown for all drugs used.

Investigation of morphofunctional cardiac parameters by means of ECHO-CG is of great interest in terms of evaluation of treatment efficacy and in terms of possible development of CHF with intact EF. Parameters of myocardial DD in patients without EF decrease are provided in Table 2.

As shown in Table 2, mean values of the LA volume index before and after the selected course of treatment did not show significant differences. This parameter did not exceed the threshold values of 34 mL/m^2 in the vast majority of patients examined. Values that exceeded the threshold were observed in 4 patients in the first group, in 3 patients in the second group, and in 8 patients in the third group.

The velocity ratio of early diastolic LV filling and blood flow in LA systole (E/A) is widely used in local and international practice as a classic parameter of DD of LV myocardium. At the same time, a tendency to the decrease in this parameter with age is shown.

Table 1. *The values of blood pressure at brachial artery in patients before therapy and after 6 months of selected therapy (indicated median, interquartile range)*

	Group 1		Group 2		Group 3	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
SBP, mm Hg	166.5 161–169	135.5 128–139	163.2 160–169	133.6 125–137	165.8 161–171	135.2 130–138
DBP, mm Hg	105.1 99–112	83.1 75–89	107.1 99–113	80.1 72–88	107.8 98–114	82.2 73–88

Table 2. *Echocardiographic parameters in patients before treatment and after 6 months of selected therapy (median, interquartile range)*

	Group 1		Group 2		Group 3	
	Before treatment	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
LA volume index, mL/m^2	30.5 25.2–33.9	29.2 25.2–33.9	30.7 25.6–33.8	28.5 24.9–33.9	31.2 25.3–34.8	28.8 25.1–33.8
EF, %	58.2 52.2–61.3	62.2±7.5 53.5–68.3	58.6 52.5–62.0	63.2 54.8–69.3	59.1 53.2–62.2	61.5 56.7–67.8
E/A	0.76 0.46–0.88	0.94*, ** 0.56–1.15	0.75 0.41–0.90	0.79 0.51–1.05	0.75 0.43–0.87	0.92*, *** 0.60–1.10
e'_{septal}	7.3 7.0–9.9	8.2 7.1–10.3	7.2 7.0–9.5	7.3 7.5–9.6	7.3 7.0–9.3	8.2 7.0–10.2
$e'_{lateral}$	10.8 10.0–15.8	12.9 10.2–13.6	10.5 10.0–12.1	10.6 10.1–12.1	10.5 10.0–12.3	12.8 10.2–14.6
E/e'_{mean}	11.8 6.2–16.8	11.2 8.2–13.2	11.2 6.1–16.2	11.4 6.3–16.2	11.5 6.3–16.4	10.2 7.2–13.2

Note: * — presence of significant differences for $p < 0.05$ before and after treatment
** — presence of significant differences for $p < 0.05$ between Group 1 and Group 2
*** — presence of significant differences for $p < 0.05$ between Group 2 and Group 3

However, according to guidelines, the threshold interval of its values is between 0.8 and 2.0. Thus, the mean values obtained demonstrate a decrease in this parameter below the threshold in all three groups before treatment. When studying the structure of groups, it was revealed that in some patients, the specified parameter, however, was in the range of standard values (5, 5, and 9 patients, respectively). Along with provided therapy, the patients treated with bisoprolol and valsartan were noted to have a significant increase in this parameter ($p < 0.05$). No significant changes were revealed in patients treated with perindopril.

The analysis of myocardial velocity parameters by the tissue Doppler ultrasound in the period of early diastolic LV filling when measured at the level of the mitral valve ring in its lateral parts and interventricular septum, showed positive, but statistically unreliable, changes in the groups treated with bisoprolol and valsartan, and practically no changes when perindopril was used. It should be noted that there was no decrease in these parameters (threshold value $e'_{septal} > 7$ cm/sec and $e'_{lateral} > 10$ cm/sec) in most patients examined before and after treatment. However, these parameters were decreased in 4, 4, and 7 patients (by groups), and they were restored to the normal values during treatment in 3, 3, and 5 from those.

The study of the E/e'_{mean} mean ratio demonstrated no significant change in all groups.

Conclusion

The results of advanced analysis of morphometric and functional echocardiogram parameters, which are DD markers, using criteria proposed by Euro-Filling Group (2017), showed presence of DD and increase in final flowing pressure (FFP) in the LV cavity only in 4, 4, and 7 patients, which was 16 %, 17.4 %, and 21.2 %, respectively by groups. At the same time, this pathological condition was observed in 20 (80 %), 18 (78.3 %), and 23 (71.9 %) patients, respectively, when using the E/A ratio, which is common in local practice. Analysis of the efficacy of the treatment revealed that in general, the positive impact was due to the change in decreased parameters in the group with the presence of DD or in the intermediate group in terms of the risk of its development (more than 50 %, or 50 % of criteria specified, respectively). DD prevalence in patients with EH significantly differs when using the most common traditional E/A criteria (up to 80 %) compared with using modern test panel (21.1 %). There is generally the same efficacy of all three drugs in terms of achieving target BP values. It has been shown that bisoprolol and

valsartan have the most pronounced effect on the morphometric parameters of the LA and intracardiac hemodynamics.

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DOI: 10.20514/2226-6704-2019-9-4-296-300 UDC 616.33-002.2

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EATING DISORDERS IN PATIENTS WITH CHRONIC GASTRITIS AND TYPE 2 DIABETES MELLITUS

Abstract

Diabetes mellitus holds one of the leading positions among the current problems of modern medicine. Despite the obvious success in studying diabetes in the last decades, its prevalence has become pandemic. In spite of the use of modern methods of therapy, a rather high frequency of diabetes mellitus complications from various organs and systems, the pathological changes in which largely determine the course of the disease and patient's quality of life remains. Issues of eating disorders and their correction play an important role in the complex therapy of patients with diabetes mellitus. **Objective:** determination of the characteristics and relationship of eating disorders with gastroenterological symptoms and glucose levels in patients with chronic gastritis in type 2 diabetes. **Materials and methods:** dynamic study of the eating behavior and quality of life in 66 patients with chronic gastritis in type 2 diabetes mellitus was conducted using GSRS, SF-36 and DEBQ questionnaires. The level of glucose on an empty stomach and after eating was also measured, the frequency of self-measurement of glucose level and the presence of diabetes mellitus complications were determined. **Results:** the identified correlation relationships suggest that gastrointestinal symptoms characteristic of chronic gastritis with type 2 diabetes mellitus worsen the physical and psychological components of health, which provokes a breakdown and a violation of the diet in this category of patients. **Conclusion:** chronic gastritis in patients with type 2 diabetes mellitus aggravates the prognosis of diabetes and exacerbates eating disorders, which requires observation of an endocrinologist, as well as a gastroenterologist and psychotherapist in the management of such patients.

Key words: *quality of life, eating behavior, chronic gastritis, type 2 diabetes mellitus*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 30.01.2019
Accepted for publication on 23.05.2019

For citation: Kazarin D. D., Shklyaev A. E., Gorbunov Yu. V. EATING DISORDERS IN PATIENTS WITH CHRONIC GASTRITIS AND TYPE 2 DIABETES MELLITUS. The Russian Archives of Internal Medicine. 2019; 9(4): 296-300. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-296-300

DM — diabetes mellitus, CG — chronic gastritis

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Introduction

For patients suffering from diabetes mellitus (DM), the issues of eating disorders are of key importance, primarily because nutritional errors worsen the control of diabetes, cause hyperglycemia, which provokes many different disorders, including angio-, retino- and polyneuropathy. In the treatise of the VIII century called Zhud-Shi it was noted that «polyuria» is more common in those patients who are prone to malnutrition and follow a low-activity lifestyle [1]. At the same time, the frequency of gastric pathology in patients with DM is higher than in the general population, and gastroenterological disorders are more or less present in the vast majority of said patients [2]. Patients with combined pathology of the upper gastrointestinal tract and endocrine system are at risk of eating disorders. The condition of the gastrointestinal tract seriously affects the processes of nutrition and eating behavior, since the endocrine cells of the gastric mucosa are a source of gastrointestinal hormones — regulators of appetite and eating behavior. Chronic gastritis (CG) is characterized by inflammatory and dystrophic changes in the gastric mucosa, leading to disorders of endocrine function and, consequently, secretion of regulatory GI hormones.

In addition, type 2 diabetes is a disease associated with an impaired action of insulin, ghrelin and leptin, which are hormones that regulate appetite and eating behavior. In the formation of insulin resistance, ghrelin levels remain elevated even after eating, leading to chronic hunger (mainly hunger for carbohydrates), excessive food intake, weight gain, and eventually — to obesity. Excess weight has a significant impact on the course of type 2 diabetes, greatly reducing the efficacy of its treatment. The presence of eating disorders affects the control of DM, so it is important for clinical specialists in the management of this group of patients [3]. In obesity, in turn, insulin resistance increases, its frequency and severity increases with the increase in the mass of adipose tissue, especially in the visceral region [1]. A pathophysiological «vicious circle» is formed. The leading factor in the development of obesity is eating disorders (ED).

Currently, there are three types of eating disorders: external, restrictive and emotional. External ED is manifested by an increased reaction of the patient not to internal homeostatic stimuli for eating (glucose level, blood free fatty acids, etc.), but to external stimuli (beautiful table, eating person, attractive food advertising) [4].

Another type of disorder is emotional ED (hyperphagic reaction to stress or emotional tension). In this case, the stimulus to food intake is not physical hunger, but psychological discomfort. Eating soothes, distracts, improves mood — in other words, serves as a «therapy» of emotional discomfort. Emotional ED can be manifested by episodes of overeating (compulsive ED), or overeating, clearly confined to the evening and night time (night eating syndrome) [5].

Another type of ED is restrictive, characterized by excessive food self-restriction, to which patients with DM are often prone [6]. The emotional imbalance that occurs during following strict diets by such patients is called dietary depression [7]. Dietary depression leads to the abandonment of further compliance with the diet and the change in period of restrictive ED with periods of overeating with a new intensive weight gain.

The issue of ED in patients with type 2 DM and CG is currently little studied, but there are some studies of ED in type 2 DM [8].

Taking into account the above, it is very important to study the eating behavior in patients with CG and type 2 DM in order to improve the efficacy of therapy for these diseases.

Objective: to determine the relationship of gastroenterological symptoms with eating disorders in patients with CG in type 2 DM.

Materials and methods

The study was conducted in the Endocrinology and Gastroenterology Departments of Budgetary Institution of the First Clinical Hospital of Ministry of Health of Udmurtia in Izhevsk.

Two groups of patients were identified: Group I — patients with CG and type 2 DM (n = 34 people), Group II — patients with CG without type 2 DM (n = 32 people). The groups were comparable in age (47.8±5.8 years in the first group, 42±6.1 years in the second group) and gender composition (6 % and 8 % of males in Group I and II, respectively). Among patients of Group I,

68.75 % (BMI >35 kg/m^2) suffered from obesity of the second and third degree, among patients of Group II — 6 %.

To verify the diagnosis of chronic gastritis all the patients underwent EGD (the Olympus fiberscope, Japan) with biopsy of the gastric mucosa. EGD was carried out in fasting condition in the morning, and patients did not take a meal for at least 6 hours and water for 2 hours before the study. Detection of Helicobacter pylori infection was carried out in the feces by a single-stage immunochromatographic assay to identify specific antigens. All patients underwent histologic examination of antral mucosa and gastric body samples. Two gastric biopsy samples were examined from each part. Biopsy samples were fixed in 10 % neutral formalin, and paraffin embedded according to the conventional method. Deparaffinized slices with thickness of 4–5 μm were stained with hematoxylin and eosin, then with slice zoom of 400 the degree of infiltration with granulocytes, mononuclear cells, as well as the presence of atrophy and/or metaplasia was determined. Pathological changes were assessed by a semi-quantitative method using visual analogue scale (VAS) in accordance with the updated Sydney System (Houston, 1994) [9].

The presence of EDs was determined using DEBQ (The Dutch Eating Behaviour Questionnaire), developed at the Faculty of Human Nutrition and the Faculty of Social Psychology in Agricultural University (the Netherlands) for the detection of restrictive, external and emotional eating behavior. The results of studies by local scientists [6, 10] confirm that DEBQ meets the criteria of validity and reliability.

Both groups also used the GSRS questionnaire on gastroenterological symptoms and the SF-36 questionnaire on quality of life, the use of which is justified in a number of works [11, 12]. Fasting and postprandial glucose levels were also measured, and the frequency of self-measured blood glucose and presence of diabetes complications were additionally determined in Group I. From patients in both groups, informed consent was obtained for examination and treatment, according to the order of the Ministry of Health of the Russian Federation No. 173/1 dated July 25, 2012 «On informed voluntary consent for medical care».

Statistical analysis was performed using IBM SPSS Statistics package for Windows version 17.0.1. Nonparametric methods of statistical processing were used, since the distribution in both samples was not normal according to the Kolmogorov-Smirnov test ($p = 0.72$ and $p = 0.94$, respectively). The reliability of the differences was determined by the U-Mann-Whitney test, correlation relationships — by the Spearman rank correlation test. The results were considered reliable at $p < 0.05$.

Results and discussion

In 100 % of patients enrolled, immunochromatographic assay revealed Helicobacter pylori infection in feces. There were changes of different degree in the gastric mucosa in all patients in both groups according to EGD. In the vast majority of patients, focal gastritis of gastric antrum or body and mucosal hyperemia were identified. In addition, some patients had signs of pyloritis, duodenitis, as well as indirect signs of gastroparesis, in particular, the presence of the food taken the day before (patients took their last meal no more than 6 hours before the endoscopic examination). The results are presented in Table 1.

Table 1. *Indicators of gastroscopic studies in patients with type 2 diabetes*

Endoscopic signs	Number of patients	
	Group I (n = 34), %	Group II (n = 32), %
Mucosal hyperemia	94±2.1	98±2.3
Focal gastritis of gastric body	82±1.4	80±1.8
Focal gastritis of gastric antrum	79±0.8	81±1.1
Pyloritis	21±1.7	23±0.9
Duodenitis	15±1.1	13±1.9
Signs of gastroparesis	34±2.2	30±1.9

Table 2. *Indicators of histological examination of biopsy samples of the gastric mucosa in patients with type 2 diabetes*

Parameter	Points on the visual analogue scale	
	Gastric body	Gastric antrum
Degree of infiltration with granulocytes	2.86±0.92	2.25±0.24
Degree of infiltration with mononuclear cells	2.03±0.36	1.74±0.41
Atrophy	1.97±0.24	0.52±0.09
Metaplasia	0	0

According to EGD results, based on U-Mann-Whitney test, no significant differences between the groups of patients were initially revealed, which indicates the comparability of the samples (U-Mann-Whitney = 18.0; p = 0.84).

According to histological data, the vast majority of patients had signs of chronic gastritis, while a small part of patients (9.8 %) had signs of atrophy. There were no changes corresponding to intestinal metaplasia of the gastric mucosa at the time of the study. The results are presented in Table 2.

Among patients of Group I, 87 % of patients had eating disorders. Structure of eating disorders in patients in Group I: restrictive type of ED (58 % of patients), external ED (49 % of patients), emotional type of ED (37.5 % of patients).

Patients in Group II were dominated by emotional type of ED — 39 %, restrictive and external types of ED were identified in 18 % and 27 %, respectively, and in general, eating disorders were observed in 36 % of patients in this group.

Eating behavior in patients of Groups I and II has significant differences in restrictive and external types (p = 0.031 and p = 0.046, respectively). Patients with CG and type 2 DM in comparison with patients without endocrine pathology are more likely to have restrictive ED. In particular, the need for a strict diet and restrictions in consumption of several products is replaced by a relapse. Also, in patients with CG and type 2 DM, in contrast to patients without endocrine pathology, there is a higher rate of ED of the external type, that is, an increased reaction to external food stimuli, regardless of hunger.

There were no significant differences between the groups in frequency of emotional ED (p = 0.39).

All the obtained results (ED, gastroenterological symptoms according to the GSRS questionnaire, quality of life assessment according to the SF-36 questionnaire, glycated hemoglobin level (HbA1c), fasting and post-meal glucose levels), as well as the frequency of self-measuring of blood glucose and the presence of diabetes complications in Group I patients were subjected to correlation analysis according to the Spearman test. In Group I, moderate direct correlation between the restrictive ED and the total rate of gastroenterological symptoms (p = 0.437 at p= 0.016), the frequency of self-measuring of blood glucose (p = 0.65 at p = 0.002) and fasting and post-meal glucose level (p = 0.63 at p = 0.003 and p = 0.613 at p = 0.0018, respectively) and the inverse correlation with the mental health component (p = –0.522 at p = 0.002) were found.

In Group II, weak direct correlations between emotional ED and total rate of gastrointestinal symptoms (p = 0.216 at p = 0.059) were revealed. The level of the "p" significance in this case allows us to speak only about the tendency to the reliability of the result and does not allow us to unambiguously exclude the error of type I ("a"). There were no other correlations according to Spearman's rank test in Group II.

Conclusion

The data of EGD and histological examination indicate that patients with type 2 diabetes often suffer from chronic gastritis, including atrophic gastritis associated with Helicobacter pylori infection, and mainly in this group of patients the gastric body is affected. At the same time, in patients who participated in the study no signs of intestinal metaplasia of the gastric mucosa were shown.

The revealed correlations suggest that gastroenterological symptoms typical for CG (abdominal pain, heartburn, bitter taste in the mouth, etc.) create

physical discomfort, which provokes a relapse and diet failure, generally, the use of a large amount of sweet, saturated with carbohydrates food. Since the diet with type 2 diabetes is quite strict (restrictive), its failure, which caused an increase in blood glucose levels, generates guilt and anxiety associated with the mental health component identified by the SF-36 questionnaire. Patients begin to self-measure blood glucose level more often, which is increased due to diet disorders, which in turn also generates anxiety and nervousness.

Thus, CG in patients with type 2 DM aggravates the prognosis of diabetes and exacerbates eating disorders in this category of patients. With the combination of CG and type 2 DM, correction of eating behavior becomes an important but difficult task. Eating disorders are associated with somatic, endocrine and psychoemotional disorders, which requires monitoring by an endocrinologist, gastroenterologist and psychotherapist in the management of this group of patients.

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DOI: 10.20514/2226-6704-2019-9-4-301-307 UDC 616.248-06:616.13-009.12-07

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AMBULATORY ARTERIAL STIFFNESS MONITORING IN PATIENTS WITH ASTHMA

Abstract

Cardiovascular disease is one of the major causes of death throughout the world. Early detection of target organ damage is important for more successful prevention of cardiovascular diseases and improvement of patient outcomes. One of these target organs is the vascular wall, and its damage consists in loss of elastic properties and increase in stiffness. Many studies have shown that the increasing stiffness of the vascular wall is an independent predictor of cardiovascular risk. **Objective:** To evaluate parameters of the ambulatory arterial stiffness monitoring in patients with bronchial asthma. **Materials and methods.** The study enrolled 119 patients with asthma. The group of control included 30 practically healthy volunteers comparable by gender and age with the patients of the main group. Each patient underwent ambulatory blood pressure and arterial stiffness monitoring using BPLab MnSDP-2 device (Petr Telegin, Russia). **Results:** In patients with asthma higher values of augmentation index, arterial stiffness index and pulse wave velocity in the aorta in comparison with patients of the control group, as well as violation of the 24-hour profile of arterial stiffness were noted. **Conclusion.** Patients with asthma demonstrated significantly increased arterial stiffness in comparison with control group.

Key words: *arterial stiffness, asthma, augmentation index, pulse wave velocity*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 02.04.2019

Accepted for publication on 17.06.2019

For citation: Karoli N. A., Zarmanbetova O. T., Rebrov A. P. AMBULATORY ARTERIAL STIFFNESS MONITORING IN PATIENTS WITH ASTHMA. The Russian Archives of Internal Medicine. 2019; 9(4): 301-307. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-301-307

ASI — arterial stiffness index, AASI — ambulatory arterial stiffness index, HT — hypertension, BA — bronchial asthma, DBP — diastolic blood pressure, AI — augmentation index, CHD — coronary heart disease, PP — pulse pressure, SBP — systolic blood pressure, ABPM — ambulatory blood pressure monitoring, AASM — ambulatory arterial stiffness monitoring, DND — degree of night decrease, PWV — pulse wave velocity, CVD — cardiovascular disease, RF — risk factors, HR — heart rate

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death worldwide. The development of CVD is a cardiovascular continuum from exposure to risk factors, progression of atherosclerosis to the development of its complications and death [1]. Accordingly, interrupting the chain of events at various stages of this continuum can prevent or delay CVD development. Risk factors (RF)

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are at the very beginning of the chain, being the trigger for the development of pathological conditions [2, 3]. Along with the main factors (hypertension, age, smoking, hypercholesterolemia, diabetes mellitus), vascular wall stiffness is considered as an independent cardiovascular risk factor [4].

Determination of stiffness is a study recommended by the Russian Medical Society for Hypertension to assess the state of the vascular wall as a target organ in CVD [5]. Increased stiffness is the culmination of pathological processes in the vascular wall, such as calcium deposition, fragmentation and reduction of elastin, increased amount of collagen. Calcification of major arteries results in increased pulse wave velocity (PWV) and, therefore, an earlier return of the reflected wave to the aorta. With rising stiffness systolic blood pressure (SBP) in the aorta increases but diastolic pressure (DBP) decreases. This leads to an increase in postload on the left ventricle, followed by the development of hypertrophy, deterioration of coronary perfusion [4].

Bronchial asthma (BA) remains a global health problem due to the annual increase in morbidity and mortality [5]. The frequent combination of BA and CVD raises interest in the study of this problem. In local medicine, studies were conducted with a single measurement of vascular stiffness in patients with asthma, and an increased PWV in patients with severe disease was revealed [6, 7]. The emergence of the possibility of measuring stiffness during the day makes it possible to identify the initial changes in the vascular wall, to assess the circadian rhythm of indicators [8, 9].

The **objective** was to study the daily profile of vascular wall stiffness in patients with BA.

Materials and methods

The open-label study enrolled 119 patients with BA (44 men and 75 women), whose mean age was 56.7 ± 8.23 years. The disease duration was 6 [4.0; 8.0] years. The diagnosis of BA was established in accordance with the generally accepted clinical, laboratory and functional criteria (GINA 2016) after spirometry. In accordance with the objective, we excluded patients with clinical signs of coronary heart disease, peripheral vascular atherosclerosis, other severe chronic diseases at the acute stage, bronchial and lung diseases of other etiology from the analysis.

The control group included 30 healthy individuals without hypertension (HT), chronic respiratory diseases, or family history of coronary heart disease (CHD). The examined persons of the control group were comparable by gender and age with the patients of the main group (Table 1).

All examined persons signed an informed consent to participate in the study.

Ambulatory blood pressure (ABPM) and arterial stiffness (AASM) monitoring was carried out using the BPLab MnSDP-2 device (Petr Telegin LLC, Nizhny Novgorod, Russia), stiffness parameters

Table 1. *Clinical pattern of patients with asthma and of the control group*

Parameters	Patients with BA, n=119	Control group, n=30	p_1
Age (years)	56.7 ± 8.23	57.14 ± 6.5	ns
Body mass index (BMI) (kg/m^2)	27.43 ± 5.12	26.79 ± 5.05	ns
Smokers, %	33.6	36	ns
Mild bronchial asthma, %	6.7	–	–
Moderate bronchial asthma, %	33.6	–	–
Severe bronchial asthma, %	59.7	–	–
Hypertension, %	69.7	–	–
Duration of hypertension (years)	5.0 [4.0; 7.5]	–	–
Systolic BP, mm Hg	134.6 ± 15.22	118.2 ± 5.55	<0.001
Diastolic BP, mm Hg	85.3 ± 8.9	75.04 ± 4.3	<0.001
FEV_1, %	67.0 [38.0; 84.0]	99.0 [78.0; 102.0]	<0.001

Note: ns — not statistically significant

were estimated by means of the Vasotens application program based on mathematical processing of pressure oscillogram records.

Among the parameters of arterial stiffness, arterial stiffness index (ASI), ambulatory arterial stiffness index (AASI), pulse wave velocity in the aorta (PWV), and augmentation index (AI) were assessed. To solve the problem of dependence of arterial stiffness on BP value and heart rate (HR), BPLab software calculates values reduced to SBP of 100 mm Hg and HR of 60 and 75 beats/min: $PWV_{100\text{-}60}$, $ASI_{100\text{-}60}$, AI_{75}.

To assess the circadian rhythm we proposed the "Method of estimating the circadian rhythm of pulse wave velocity in aorta" (rationalization proposal No. 2993 dated 20.03.2018) based on the determination of the degree of night decrease (DND in PWV) by the formula: the ratio of the difference between the average daily and average night parameters of PWV to the average daily parameters, expressed as a percentage:

$$\text{DND in PWV} = \{[\text{PWV (d)} - \text{PWV (n)}] / \text{PWV (d)}\} \times 100\ \%$$

Normal values were determined based on the study results for arterial stiffness in healthy individuals. The range of normal values was defined as the range of measurements consisting of two quartiles above and below the median. Thus, the range includes the central 50 % of all measurements and determines the "normal" boundaries of DND in PWV in the aorta from 11 to 18 %.

Statistical analysis was performed using STATISTICA 10.0 (StatSoft) software package. To check the conformity of parameter distribution with normal distribution, the Shapiro — Wilk test was used, and normal distribution was considered with $p>0.05$. For the description of normally distributed quantitative parameters, the mean value of parameter and standard deviation (M ± SD) were used; for the description of parameter distribution different from the normal, the median (Me), upper and lower quartiles were indicated [Q25; Q75]. To compare two groups with normal distribution of the quantitative parameter, Student's t-test for independent groups was determined. The correlation of two normally distributed quantitative parameters was studied using the Pearson method. When the distribution deviated from normal distribution, the Mann — Whitney test was used to compare the significance of intergroup differences in quantitative values, and the Spearman method was used to analyze the association of qualitative parameters. The differences were considered as statistically significant at $p<0.05$.

Results

In the study of the daily vascular wall stiffness parameters, their statistically significant increases were found in patients with BA (Table 2). According to guidelines of European Society of Cardiology and European Society of Hypertension, PWV >10 m/s is a risk factor for cardiovascular events [4]. Our study revealed an increase in the average daily, daily and night PWV, and values of more than 10 m/s were reported in 43 (36.1 %) patients with BA and only in 6 (5 %) patients of the control group ($p<0.001$).

AI is the ratio of direct and reflected pulse waves passing through the vascular wall. Normally, the reflected component is always less than a direct one, and AI value is negative. In the case of increased vascular stiffness, the reflected component may exceed the direct one, and AI value becomes positive [10]. The increase in the reflected wave velocity leads to its early return to the aorta, during the systole period, which results in increased systolic BP (SBP), pulse pressure (PP), post-loading on the left ventricle, decreased diastolic BP (DBP), and, therefore, a deterioration in coronary perfusion [11]. Our study found 24-hour, day and night increase in AI in patients with BA compared to the values of similar parameters in healthy individuals. The given parameters of AI_{75} (24-hour, day, night), $ASI_{100\text{-}60}$ (24-hour, day), $PWV_{100\text{-}60}$ in the aorta (24-hour, night) in the patients keep increasing compared with the values of these parameters in healthy individuals, which confirms the higher arterial stiffness in patients with BA regardless of BP and HR values.

The inclusion of algorithms for determining arterial stiffness in ABPM devices makes it possible to estimate 24-hour changes of parameters [12]. It was found that ASI, $ASI_{100\text{-}60}$, AI and AI_{75} at night were higher than in the daytime ($p<0.05$), which indicates an increase in arterial stiffness at night.

Table 2. *Parameters of ambulatory arterial stiffness monitoring in patients with asthma and of the control group*

Parameters	Patients with BA, n=119	Control group, n=30	p_1
	24 hours		
PWVao, m/s	9.74 ± 1.73	9.12 ± 1.23	=0.0023
$PWVao_{100-60}$, m/s	9.14 ± 1.87	8.59 ± 1.55	=0.014
AI, %	–21.14 ± 22.54	–25.62 ± 17.23	=0.03
AI_{75}, %	–24.32 ± 20.16	–28.31 ± 21.71	=0.024
ASI	129.4 [124.0; 159.0]	118.5 [108; 124]	=0.012
ASI_{100-60}	119.0 [105.0; 159.0]	109.0 [95.0; 112.0]	=0.02
AASI	0.30 ± 0.18	0.31 ± 0.18	ns
DND in PWVao, %	8.5 [5.5; 11.5]	11.5 [9.5; 14.5]	=0.032
	Awake		
PWVao, m/s	9.86 ± 1.76	9.25 ± 1.22	<0.001
$PWVao_{100-60}$, m/s	9.02 ± 2.49	8.72 ± 1.46	ns
AI, %	–20.56 ± 19.53	–28.26 ± 18.63	<0.001
AI_{75}, %	–24.38 ± 21.35	–31.35 ± 19.43	=0.0041
ASI	119.0 [121.0; 155.0]	109.0 [91.0; 131.0]	=0.021
ASI_{100-60}	107.0 [97.0; 142.0]	98.5 [89.0; 122.0]	ns
	Asleep		
PWVao, m/s	9.34 ± 1.73	8.98 ± 1.19	=0.045
$PWVao_{100-60}$, m/s	8.97 ± 2.16	8.46 ± 1.28	=0.028
AI, %	–17.52 ± 24.5	–25.46 ± 28.34	=0.012
AI_{75}, %	–23.46 ± 23.15	–33.96 ± 37.46	=0.0023
ASI	132.0 [123.0; 181.0]	122.5 [106.5; 138.5]	=0.042
ASI_{100-60}	117.0 [95.0; 166.0]	109.0 [90.0; 128.0]	ns

Note: ns — not statistically significant

This is confirmed by the value of the degree of night decrease in PWV, which in patients with BA (8.5 [5.5; 11.5]) was significantly lower than in the control group (11.5 [9.5; 14.5], p=0.032). Abnormal DND in PWV in the aorta was found in 48 (40.3 %) patients with BA and only in 5 (16.6 %) people in the control group.

In this study, it was found that the increase in vascular wall stiffness is associated with clinical and functional parameters. Thus, BA severity correlated with PWV per day (r=0.46, p=0.001), PWV_{100-60} per day (r=0.36, p<0.001), ASI per night (r=0.3, p=0.008) and ASI_{100-60} per day (r=0.35, p=0.023). Increase in PWV at night (r=0.33, p=0.003) was associated with the increase in the number of BA exacerbations over the past 12 months. The number of points obtained in the AST questionnaire had a moderate negative correlation with PWV and PWV_{100-60} per day (r=–0.56, p<0.001 and r=–0.62, p<0.001, respectively) and in daytime hours (r=–0.5, p=0.001 and r=–0.43, p=0.001, respectively).

The dependence of vascular stiffness parameters on age, BMI, cholesterol levels and smoking has been proven in numerous studies. Patients with asthma also showed an increase in PWV per 24 hours (r=0.32, p=0.021) and day (r=0.34, p=0.014), PWV_{100-60} per day (r=0.39, p=0.009) with increasing age. The relationship between body mass index (BMI) and AI per day (r=0.36, p=0.001), PWV per 24 hours (r=0.68, p<0.001), day (r=0.66, p<0.001) and night (r=0.73, p<0.001) was revealed. Average night AI_{75} values were correlated with an index in pack-years (r=0.32, p=0.004). With an increase in cholesterol levels, there was an increase in the average daily (r=0.39, p<0.001) and average night (r=0.37, p=0.001) values of ASI_{100-60}.

The most common concomitant disease in patients with BA is HT. The combination of the two diseases was found in 35 % of patients. In order to analyze the effect of concomitant hypertension on vascular wall stiffness, patients were divided into 2 groups depending on the presence of HT. The first group

Table 3. *Clinical pattern of patients with asthma with and without hypertension*

Parameters	BA and HT, n=83	BA without HT, n=36	Control group, n=30
Age (years)	57.54 ± 9.18	56.82 ± 9.54	57.14 ± 6.5
Body mass index (BMI) (kg/m²)	28.26 ± 4.34*#	26.92 ± 5.02	26.79 ± 5.05
Mild bronchial asthma, %	3.6	13.9	–
Moderate bronchial asthma, %	24	55.6	–
Severe bronchial asthma, %	72.4	30.5	–
Hypertension, %	100	–	–
Duration of hypertension, years	6.32 ± 8.2#	–	–
Systolic BP, mm Hg	134.8 ± 10.4**##	123.4 ± 6.1	118.2 ± 5.55
Diastolic BP, mm Hg	83.6 ± 9.1**#	78.12 ± 4.7	75.04 ± 4.3

Note: Statistically significant differences with the control group: * — p<0.05, ** — p<0.01, *** — p<0.001; with group 2: # — p<0.05, ##### — p<0.01, ### — p<0.001

Table 4. *Parameters of ambulatory arterial stiffness monitoring in patients with asthma with and without hypertension*

Parameters	BA and HT, n=83	BA without HT, n=36	Control group, n=30
	24 hours		
PWVao, m/s	10.09 ± 1.82*#	9.28 ± 1.82	9.12 ± 1.23
$PWVao_{100-60}$, m/s	9.38 ± 1.96*#	8.78 ± 1.73	8.59 ± 1.55
AI, %	–15.84 ± 16.94***##	–23.61 ± 17.6	–25.62 ± 17.23
AI_{75}, %	–22.78 ± 18.43*#	–27.45 ± 18.52	–28.31 ± 21.71
ASI	134.0 [118.0; 148.0]**#	124.0 [116.0; 132.0]*	118.5 [108; 124]
ASI_{100-60}	120.5 [108.0; 139.0]**#	114.0 [101.0; 129.0]	109.0 [95.0; 112.0]
AASI	0.3 ± 0.17	0.29 ± 0.19	0.31 ± 0.18
DND in PWVao, %	8.0 [5.5; 10.0]***##	10.5 [7.0; 12.5]*	11.5 [9.5; 14.5]
	Awake		
PWVao, m/s	10.13 ± 1.81*#	9.36 ± 2.1	9.25 ± 1.22
$PWVao_{100-60}$, m/s	9.65 ± 2.09*#	8.92 ± 1.93	8.72 ± 1.46
AI, %	–17.11 ± 17.4***##	–24.92 ± 18.2*	–28.26 ± 18.63
AI_{75}, %	–23.38 ± 19.52**#	–28.36 ± 19.1*	–31.35 ± 19.43
ASI	126.0 [120.0; 149.0]*#	118.0 [112.0; 141.0]*	109.0 [91.0; 131.0]
ASI_{100-60}	117 [97.0; 124.0]*#	109 [91.0; 124.0]*	98.5 [89.0; 122.0]
	Asleep		
PWVao, m/s	9.87 ± 1.86*#	9.14 ± 1.92*	8.98 ± 1.19
$PWVao_{100-60}$, m/s	9.24 ± 1.56*#	8.54 ± 2.42	8.46 ± 1.28
AI, %	–14.73 ± 15.41*#	–21.72 ± 21.14*	–25.46 ± 28.34
AI_{75}, %	–21.82 ± 20.1*#	–26.53 ± 22.72*	–33.96 ± 37.46
ASI	135.5 [122.0; 152.0]**#	128.0 [121.0; 149.0]*	122.5 [106.5; 138.5]
ASI_{100-60}	126.0 [97.0; 146.0]*#	114.0 [99.0; 136.0]	109.0 [90.0; 128.0]

Note: Statistically significant differences with the control group: * — p<0.05, ** — p<0.01, *** — p<0.001; with BA patients without HT: # — p<0.05, ##### — p<0.01, ### — p<0.001

consisted of 83 patients with BA with HT, the second one — 36 patients without HT (Table 3).

It was noted that vascular wall stiffness increased in patients with BA regardless of the presence or absence of HT, but changes in PWV and AI per 24 hours, day and night were more significant in patients with HT (Table 4).

DND in PWV was calculated for all of the subjects. In patients with a combination of BA and HT, pathological DND in PWV in the aorta was revealed

in 41 (49.4 %) patients, in 7 (19.4 %) patients with BA without HT and in 5 (16.6 %) patients of the control group.

In the study of the above parameters in patients with BA and HT elevated values of AI_{75} (24 hours, day, night), ASI_{100-60} (24 hours, day, night), $PWVao_{100-60}$ (24 hours, day, night) remained in comparison with patients with BA without HT and individuals in the control group.

The correlation of ASI_{100-60} per 24 hours ($r=0.37$, $p=0.001$) and night time ($r=0.32$, $p=0.004$) with the duration of HT was noted.

Discussion

Despite significant advances in understanding the pathogenesis of BA and the development of new drugs, in real clinical practice, challenges in the achievement of complete disease control remain. One of the reasons hindering control is the presence of concomitant diseases, including of the cardiovascular system. The results of recent studies show that the combination of BA and CVD is increasingly common in routine clinical practice, due to both increased incidence of CVD and BA, and an increase in the geriatric population of patients.

According to meta-analysis data, including 11 studies (117,548 patients with BA and 443,948 persons of the control group), cardiovascular and cerebrovascular diseases, including CHD, myocardial infarction, HT, stroke, arrhythmias, atrial fibrillation and heart failure are more common in patients with asthma [13].

The modern concept of CVD development, which is understood as the continuous development of CVD from risk factors to the development of chronic heart failure, implies the possibility of correcting changes already at the stage of identifying risk factors. Arteries are one of the main organs that are affected by CVD risk factors. In the literature, there is a large number of works devoted to the study of changes in the structure and metabolism of the arterial wall under the influence of CVD risk factors. However, most of them were carried out in patients with existing CVD, so the question on the state of the walls of the major arteries in the presence/absence of CVD risk factors in practically healthy (with respect to the cardiovascular system) persons remains relevant. Based on the requirements for CVD prevention, modern non-invasive diagnosis of the state of artery walls should facilitate screening studies. The methods used should be reproducible, independent of the researcher, allow comparison of data obtained in different research centers, and ensure the fullest possible compliance of the obtained arterial wall stiffness parameters with histological data. Automated systems for determining the biomechanical properties of arteries based on the principles of sphygmography are of great interest to researchers. One of the most commonly used parameters of arterial wall stiffness is PWV.

Earlier studies have demonstrated an increase in the stiffness of the vascular wall in patients with BA in the case of single measurement. In the study by Demko I. V. (2013), 204 patients with moderate and severe BA in the exacerbation period and over the time after 12 months were evaluated for arterial stiffness, and increase in PWV and AI values was revealed in patients with BA both in the period of exacerbation and in remission. It was noted that stiffness parameters correlated with oxygen saturation, disease severity, and clinical symptom severity [6]. The results of our study confirm the previously obtained data in patients with BA; an increase in vascular wall stiffness was found in patients with BA, and correlation of disease severity with PWV was also noted.

In previous studies, it was found that obesity contributes to vascular wall stiffness [6]. In our study, a positive correlation between arterial stiffness and BMI and other classical CVD factors (cholesterol level, age) was found.

Analyzing the status of arterial mechanical properties in patients with BA depending on the presence or absence of HT, it was found that the presence of HT worsens the elastic properties of the vascular wall: in hypertensive patients, changes in PWV and AI were more significant than in patients without hypertension. Correlation of vascular stiffness with duration of HT was revealed.

Sobko E. A. (2012), in her study with a single measurement of stiffness parameters, found that an increase in arterial stiffness is observed regardless of the presence of concomitant HT in patients with BA, but the greatest changes were detected in patients with high blood pressure [14]. The advantage of ambulatory vascular stiffness monitoring is the ability to assess circadian rhythm of parameters. In the patients examined by us, there was a

tendency of night increase in vascular stiffness, accompanied by insufficient DND in PWV, which may be the result of the negative effect of night bronchial obstruction attacks.

In the study by Sobko E. A. et al. (2012), the severity of systemic inflammation was a predictor of increased vascular stiffness [14]. The data obtained by the authors indicate that an increase in serum levels of proinflammatory cytokines (sPECAM-1/sCD31) during the period of BA exacerbation leads to an increase in PWV (r=0.517, p=0.008) [13]. Our study revealed a positive correlation between the number of asthma exacerbations and PWV, which indirectly confirms the relationship between systemic inflammation and increased vascular stiffness.

Conclusions

In patients with bronchial asthma, there was an increase in vascular wall stiffness, an increase in PWV and AI values for 24 hours, day and night, and AI values per night were higher than daily values, which indicates an increase in arterial stiffness at night. The presence of concomitant HT leads to an increase in vascular wall stiffness. Given the proven prognostic value of arterial stiffness parameters, their study in patients with BA will allow to assess cardiovascular risk earlier.

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DOI: 10.20514/2226-6704-2019-9-4-308-312 UDC 616.1/.7-002.182-08

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LOFGREN'S SYNDROME: CLINICAL CASE

Abstract

Sarcoidosis is an inflammatory disease characterized by the formation of non-necrotising granulomas in various organs and tissues. The clinical signs of sarcoidosis are determined by the number of affected organs, the degree of their structural and functional impairment, and the severity of inflammatory symptoms. The article presents a clinical observation of one of the forms of sarcoidosis — Lofgren's syndrome, which is characterized by a triad of intrathoracic lymphadenopathy, acute arthritis and erythema nodosum. The diagnosis was confirmed histologically. Under the prescribed treatment, signs of acute inflammation reversed and the patient's state improved. The authors emphasize that they do not recommend widespread use of systemic glucocorticosteroids in patients with this disease, since their use may be associated with its relapsing course.

Key words: *Lofgren's syndrome, sarcoidosis, acute arthritis*

Conflict of interests

The authors declare no conflict of interests.

Source of financing

The authors state that no finding for the study has been received.

Article received on 28.03.2019

Accepted for publication on 08.07.2019

For citation: Shklyaev A. E., Semyonovykh E. A., Ivanova L. V. et al. LOFGREN'S SYNDROME: CLINICAL CASE. The Russian Archives of Internal Medicine. 2019; 9(4): 308-312. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-308-312

Sarcoidosis is an inflammatory disease characterized by the formation of non-necrotising granulomas in various organs and tissues. Inflammation is modulated by the monocyte-macrophage system cells and lymphocytes, and can have a different degree of severity [1].

The clinical signs of sarcoidosis are determined by the number of affected organs, the degree of their structural and functional impairment, and the severity of inflammatory symptoms. Most often, intrathoracic lymph nodes, lungs, skin and eyes are involved in the process. Damage to the musculoskeletal system is less common. About 10–15 % of patients with sarcoidosis have an associated arthropathy [2].

Acute sarcoid arthritis most often is manifested as part of Lofgren's syndrome characterized by the triad of intrathoracic lymphadenopathy, acute arthritis and erythema nodosum. Acute arthritis is predominantly oligoarticular (87 %), symmetrical (76 %), and most often involves ankle joints (>90 %), usually both, as well as other larger joints of the lower limbs, therefore it is often mistaken for reactive arthritis [3]. As an example, we would like to present our own clinical observation.

Clinical case

Patient L., 31 years of age, was admitted to the hospital on 20/08/2018 with complaints of intermittent, migrating, aching pain in ankle, knee, radiocarpal joints and metatarsophalangeal joints of toes 3–5 of the left foot. There was no pain in the morning after waking up but the pain increased

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during movement, its intensity progressed during the day and reached a maximum in the first half of the night, which resulted in nocturnal sleep disturbances. Pain intensity was 5–6 points on a visual analogue scale (VAS). No morning stiffness was observed. Also, he experienced a cracking sound during movement in the knee joints and right radiocarpal joint, as well as swelling and local hyperthermia of ankle joints. He suffered from pain in lumbar and cervical regions of the spine towards evening and after exertion throughout the day. He experienced a rise in body temperature up to 37.4–37.6 °C (with maximum of 38.6 °C) by 3.00 p. m., after prolonged load on joints (walking), temperature was normalized after taking naproxen and paracetamol. He lost 3 kg within the last month, without loss of appetite.

The patient considers himself sick since 01/08/2018, when he experienced hyperemia, swelling, and local hyperthermia of the ankle joints in the morning, after getting out of bed with increasing pain in these joints. He had no catarrhal signs or sore throat. On the next day, temperature rose to 37.4 °C, injection of scleral vessels occurred. He sought medical attention at his health service provider on 03/08/2018, was followed up with diagnosis of ARVI and treated with Anaferon without effect.

Due to injection of scleral vessels, he was referred to the ophthalmologist, who made a diagnosis: episcleritis of both eyes. From 06/08/2018 he was treated with amoxicillin prescribed by a general practitioner. Laboratory data dated 07/08/2018: ESR: 30 mm/hour; WBC: 8.4×10^9/L, RBC: 4.19×10^{12}/L, HB: 129 g/L, segmented neutrophils: 79.1 %, lymphocytes: 15.6 %; monocytes: 5.3 %; PLT: 263×10^9/L.

On 08/08/2018, he was examined by a rheumatologist, on whose recommendation the following tests were performed on 10/08/2018: PCR for HLA-B27, passive hemagglutination test for detection of *Yersinia* species, *Salmonella* species, *Shigella* species, PCR for *Chlamydia* species, *Mycoplasma* and *Ureaplasma* species, EIA for HBV, HCV, HIV were negative; antistreptolysin O: 70.7 U/mL, CPK: 95 U/mL. Ultrasound scanning of visceral organs on 10/08/2018: No abnormalities were discovered. ECHO-CG dated 16/08/2018: Sizes of the cardiac chambers were normal, the valvular heart apparatus without abnormalities, the left ventricle contractility was satisfactory, ejection fraction was 75 %. The patient took naproxen when body temperature was elevated, as recommended by the rheumatologist. No significant improvement of the patient's condition was observed, low-grade fever persisted. On 20/08/2018, he was electively admitted in the rheumatology department for examination and treatment.

On physical examination at admission: Patient's gait was sparing. The symptom of lateral compression of the foot was positive at the left side. The metatarsophalangeal joints of toes 3-5 of the left foot were tender on palpation. The plantar fascia of both feet, Achilles tendons, and their points of attachment to the calcaneus bones were tender on palpation. The left Achilles tendon was swollen. Ankle joints: were swollen, circumference of the left joint was 28 cm, circumference of the right joint was 27 cm, the joints were tender on palpation, had a full range of motion. Knee joints: had no visual abnormalities, were tender on palpation in the projection of the left joint space, the range of motions in the knee joints was not restricted, the popliteal fossae were tender at maximum flexion of both knee joints. Hip joints: movements were nontender, not restricted. Small joints of the hands were looking normal and were nontender. The patient closes the hand into a fist completely, hand grip strength is sufficient. Radiocarpal joints: were painful, not swollen, symmetrical, range of motions was normal. The elbow and shoulder joints were nontender on palpation, the range of motions was complete, and the motions were painless. No tenderness on palpation of the paravertebral points and spinous processes was observed.

Investigations

On admission: WBC: 7.9×10^9/L; RBC: 4.3×10^{12}/L; HB: 130 g/L; PLT: 476×10^9/L, ESR: 69 mm/hour; AST: 15.0 U/L, ALT: 12.0 U/L, total protein: 85.0 g/L; albumin: 46.0 g/L; glucose: 5.3 mmol/L; cholesterol: 4.9 mmol/L; sodium: 143.0 mmol/L; potassium: 3.9 mmol/L; urea: 6.4 mmol/L; uric acid: 285 μmol/L; creatinine: 82.0 μmol/L; total bilirubin: 17.5 μmol/L; prothrombin time: 13.4 sec, PI: 80 %; fibrinogen: 7.0 g/L; rheumatoid factor: 3.0 U/L; antistreptolysin O: 96.0 U/mL. Immunogram: IgA:

2.7 g/L; IgM: 0.9 g/L; IgG: 11.6 g/L; C3: 135.4 mg/dL; C4: 26.4 mg/dL; CIC: 219.3 U/mL; the procalcitonin test is negative. Urinalysis: yellow, clear, specific gravity: 1,030 g/L; protein: 0 g/L; WBC: 0–1 per field of view; pH: 6.0.

Clinical signs of joint disease necessitated radiologic imaging. Frontal X-ray of the hands and feet on 21/08/2018: No bone pathology was revealed. Sacroiliac joint X-ray on 22/08/2018: there was no evidence of sacroiliitis, subchondral sclerosis was discovered on the left side. Ultrasound scanning of the knee joints on 21/08/2018: there were signs of bilateral gonarthrosis and increase in the amount of synovial fluid of the upper and lateral recesses on both sides. Ultrasound scanning of ankle joints on 22/08/2018: signs of tendonitis were discovered in the left lateral ligament. Lumbosacral spine MRI on 27/08/2018: There were no abnormalities of the spinal cord and intervertebral discs of the lumbosacral spine, there was a perineural arachnoid cyst at the S2 vertebra level, there was no evidence of sacroiliitis.

In the rheumatology department, the patient received 100 mg of nimesulide 2 times a day upon admission, with a moderate effect: there was a decrease in pain, persistent low-grade fever with a periodic increase in the body temperature to febrile levels. Due to the lack of effect of oral NSAIDs, high clinical and laboratory disease activity, two drip intravenous infusions of methylprednisolone 250 mg (23/08, 24/08/2018) were given to the patient with a good effect for the period of administration: normalization of the body temperature was observed, there were no pains in the joints, and their swelling decreased.

Erythema nodosum, severely tender on palpation, that appeared on the lateral surface of the right shin on 28/08/2018, allowed to suspect Lofgren's syndrome. CT scanning of the chest was performed on 29/08/2018 to reveal the third component of the characteristic triad. Conclusion: The lungs were pneumatized. Lung tissue density was 850 HU. The pulmonary pattern was slightly thickened due to peribronchial fibrosis and interstitium. Bronchi were patent, with no signs of local dilation; bronchial walls were indurated. In both lungs (predominantly in the upper parts), foci measuring 2–3 mm which were partly confluent were visualized around the lymphatic vessels. The structure of the pulmonary hila was defined perfectly, slightly dilated due to lymph nodes. The pleura and interlobar fissures were not changed. Lymph nodes: paraaortic, paratracheal, bifurcation, peribronchial, bronchopulmonary lymph nodes were enlarged to 12–13 mm on the short axis. Conclusion: CT signs of sarcoidosis, stage 2, mediastinal-pulmonary form.

From 31/08/2018, due to renewed pain in the joints, low-grade fever, regarded as extrapulmonary presentation of sarcoidosis, oral methylprednisolone was prescribed at a dose of 8 mg per day. The patient was discharged on 10/09/2018 with improvement: pain in the joints decreased significantly, ankle joint swelling subsided. Low-grade fever persisted.

The patient was referred to the Republican Clinical Tuberculosis Hospital with diagnosis of sarcoidosis, stage 2, Lofgren's syndrome, in order to rule out tuberculosis infection and confirm the diagnosis, where a video-assisted thoracoscopic biopsy of mediastinal lymph nodes was performed. Histological study: The lymph node tissue was subtotally replaced by epithelioid cell granulomas with giant Pirogov — Langhans cells, had no signs of necrosis, and had so-called "stamped appearance". A number of granulomas were surrounded by annular fibrosis peripherally. Conclusion: This histological pattern was more consistent with sarcoidosis.

The following recommendations were given to the patient at discharge: treatment with oral glucocorticoids and antioxidants under the supervision of a pulmonologist, follow-up by a general practitioner at the community-based facility, helical CT of the chest and abdominal ultrasound in 6 months.

Conclusion

In the clinical case presented, a young man went to a clinic with a primary lesion of ankle joints, which in combination with the erythema nodosum which appeared later, agrees with the data of other authors. A prospective cohort study of patients with recent arthritis showed that the persistence of symptoms for less than two months, symmetrical ankle arthritis and age younger than 40 years had high sensitivity (85 %) and specificity (99 %) in sarcoid arthritis. Therefore, the next step in the diagnostic search for the young man with acute,

bilateral arthritis of the ankle joints with or without painful, red nodules on the shins, is the use of diagnostic radiology exams to detect intrathoracic lymphadenopathy [4], which was performed in our patient.

The patient was discharged with significant improvement in well-being. However, the treatment performed should not be recommended for widespread use. When choosing a treatment method for a patient with sarcoidosis, systemic glucocorticosteroids (GCS) should be used with caution, since, according to literature data, recurrent course of the disease in patients with Lofgren's syndrome who took GCS was 33.3 % more frequent than in those who did not take these drugs [5]. Young age, acute onset of the disease, the presence of Lofgren's syndrome are favorable prognostic factors of sarcoidosis in this patient [6].

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COMMENTARY ON THE ARTICLE «LOFGREN'S SYNDROME: CLINICAL CASE»

Commentary written after reading an article may seem negative and overly strict. But this is far from the case. The purpose of the commentary is to analyze the logic of action so that in such cases the physician will be guided by modern knowledge of sarcoidosis. A series of monographs on sarcoidosis has been published in Russia, national clinical guidelines have been prepared, where the algorithms for diagnosing and treating this disease are quite clearly presented. However, in real clinical practice, the management of patients with sarcoidosis is not based on these provisions, but is a result of the intuition of the physician faced with such a patient.

The case presented is of great practical interest for a number of reasons. Firstly, in recent years, the number of cases of sarcoidosis has increased (probably due to both real growth and improved diagnostics). Secondly, the clinical signs of sarcoidosis are very diverse, and of these, the acute forms — Lofgren's syndrome and Heerfordt — Waldenstrom syndrome — are associated with the greatest diagnostic and therapeutic errors, and thirdly, the attitude to the use of systemic glucocorticosteroids in rheumatology and in the treatment of sarcoidosis is not equivalent and has various effects.

The diagnostic path of the patient in this clinical observation, as well as the sequence of drug use, are quite typical.

As noted in the clinical case, before making the first diagnosis, the patient had already taken naproxen and paracetamol due to articular syndrome, and achieved relief.

The first diagnosis was ARVI, acute respiratory viral infection. At the same time, the authors noted that the patient had no catarrhal symptoms, sore throat, rhinitis, cough, so, there were no respiratory symptoms. The symptom complex included low-grade fever, articular syndrome, and injection of scleral vessels. Anaferon was prescribed to the patient, which is a drug which simulates the humoral and cellular immune response, affecting the system of endogenous interferons and associated cytokines, inducing the formation of "early" endogenous interferons. The authors noted that there was no clinical response — an improvement in the condition — to this treatment. It should be noted that the described mechanism of action of this immunomodulator partially overlaps with the stages of the sarcoidosis pathogenesis. The sarcoid reaction in patients receiving interferons has been repeatedly described in literature. It is possible that the use of an immunomodulator could play a negative role in the further progression of symptoms.

Prescription of aminopenicillin by an ophthalmologist due to the diagnosed episcleritis probably corresponded to protocols in ophthalmology practice. The drug effect is not presented in the clinical case. Amoxicillin could not have any effect on the course of sarcoidosis. At least, there are no published data on the effect of aminopenicillins on the course of sarcoidosis.

At the next stage, the rheumatologist carefully examined the patient in a number of aspects, except for respiratory and phthisiological ones. Contradictory information is provided regarding the nimesulide prescribed. It has been noted that the drug eased the pain, but did not prevent rise in body temperature. At the rheumatology department, these changes were evaluated as a lack of effect, and, without further examination (at least, fluorography, search for an infectious cause of fever), high intravenous doses of systemic glucocorticosteroids were prescribed to the patient. The question arises, what are the indications for intravenous administration to a patient who is able to take drugs per os? Why was radiological lung exam not performed on a patient who was admitted with fever before prescribing such potent immunosuppressive therapy?

The authors evaluate the effect of steroids as fast and positive: arthralgia disappeared, temperature returned to normal. But four days after two infusions of methylprednisolone, the patient developed an erythema nodosum. That is, steroids have not stopped the disease. The appearance of erythema nodosum led physicians to the idea of Lofgren's syndrome, and X-ray computed tomography was performed, intrathoracic lymphadenopathy and limited dissemination were revealed. A systemic glucocorticosteroid was prescribed to the patient again. With this immunosuppressive therapy, the patient was referred to an antituberculosis institution for video-assisted thoracoscopic biopsy. The question arises, was it possible for such a patient to be referred for a biopsy to a non-antituberculosis institution, without exposing him to an undue risk of infection? If the diagnosis of sarcoidosis was originally discussed, then referring the patient to the antituberculosis institution is not logical, the VIII group of dispensary observation of patients with sarcoidosis in anti-tuberculosis institutions was abolished in Russia in 2002. If the tuberculous nature of the lesion was suspected, then why were systemic steroids prescribed without an initial TB examination? In the clinical case, we do not find any information about conducting tuberculin skin tests or PCR diagnostics before prescribing hormones.

The following recommendation of long-term use of systemic glucocorticosteroids is consistent with the provisions of the International Statement on Sarcoidosis of 1999 and Russian clinical guidelines, since only long-term use of prednisolone or its analogs can achieve cure or lasting remission. But the same documents do not include Lofgren's syndrome to the indications for steroid therapy. The recommendation of the follow-up examination after 6 months also does not comply with these documents. Early (after 3 months) assessment of the effect of hormonal drug therapy is needed in order to switch to alternative drugs if there is lack of effect without exposure to the risk of Cushing's syndrome and other consequences of long-term use of adrenal hormones.

The case presented is of great practical importance, and gratitude should be given to the authors for reporting it. The publication suggests the need to increase knowledge of sarcoidosis among doctors of various specialties. This acquires special meaning nowadays, when clinical guidelines are becoming the main guiding document for physicians.

DOI 10.20514/2226-6704-2019-9-4-313-315 UDC 616.5-002.524: 616-005.6

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ISCHEMIC STROKE IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SECONDARY ANTIPHOSPHOLIPID SYNDROME

Abstract

The article presents a clinical case of an onset of antiphospholipid syndrome in a patient with systemic lupus erythematosus and ischemic stroke. Systemic lupus erythematosus is a non-modifiable risk factor for ischemic stroke.

Key words: *risk factors, ischemic stroke, systemic lupus erythematosus, antiphospholipid syndrome*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 18.04.2019 г.

Accepted for publication on 19.06.2019 г.

For citation: Nikitenko P. S., Goryacheva S. A., Nikitenko S. V. et al. ISCHEMIC STROKE IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SECONDARY ANTIPHOSPHOLIPID SYNDROME. The Russian Archives of Internal Medicine. 2019; 9(4): 313-315. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-313-315

BP — blood pressure, APS — antiphospholipid syndrome, IS — ischemic stroke, SLE — systemic lupus erythematosus

The main causes of ischemic strokes (IS) are considered hypertension, atherosclerosis, cardiac disorders, diabetes mellitus. However, sometimes a key role in the development of "vascular catastrophe" can be played by rarer causes, such as autoimmune diseases.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology characterized by hyperproduction of organ-specific autoantibodies to various components of the cell nucleus with the development of immune inflammatory damage to tissues and internal organs. Below is a clinical case, a feature of which is the development of IS due to secondary antiphospholipid syndrome (APS), outside the clinical signs of SLE activity.

A female patient, 48 years old, was admitted to hospital with complaints of pronounced weakness in the left extremities, impaired speech quality. "Classic" vascular risk factors (smoking, alcohol abuse, hypercholesterolemia and others) could not be identified. From medical history it is known that patient A. suffers from SLE for a long time, for treatment of which she takes prednisolone in a daily dose of 2.5 mg for the last 8 years. There were no previous thrombotic episodes. In addition, for the correction of blood

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pressure (BP) she takes Diroton at a dose of 2.5 mg once a day. BP variations began to raise concerns during therapy with corticosteroids. The highest BP was 140/90 mm Hg. According to the patient, in the middle of the day she felt sick; while trying to get up, she fell, unable to keep her balance. Witnesses called the ambulance team, and she was hospitalized in the Neurological Department for patients with acute cerebrovascular accident. On admission, the patient's condition was assessed as severe. Her somatic status was stable. BP was 160/90 mm Hg. Heart rate was 68 bpm. Respiratory rate was 18 breaths per minute. According to neurological examination, her consciousness is clear. Regarding cranial nerves function, the smoothness of the nasolabial fold on the left and the deviation of the tongue to the left were determined. No movement in the left extremities was revealed. Anisoreflexia, S > D. Positive pathological reflexes (carpal Rossolimo sign, Babinsky reflex) were revealed on the left. In the rest, state with no features. According to laboratory examination methods, the following changes were revealed: hemoglobin 111 g/l, hematocrit 32.7 %, platelets 128×10^9/l, fibrinogen 5.4 g/l, ESR 20 mm/h. Lupus anticoagulants: the result is doubtful, 1.2 (norm <1.2) in the confirming test; anti-DNA antibodies are found: COI 163.5 (norm up to 25), anti-cardiolipin Abs 50.38 (norm up to 10 U/ml). ECG: sinus rhythm, increased load on the left ventricle, diffuse changes in myocardium. Spiral brain computed tomography revealed a violation of cerebral circulation of ischemic nature in the right parietal, frontal and temporal lobes. According to the results of duplex scanning, brachiocephalic arteries are passable, additional formations in the arteries were not revealed. Due to closed ultrasonic temporal acoustic windows, the study of the intracranial arteries is impossible. By echocardiography, no abnormalities, the ejection fraction is 64 %. Consultation was performed, and the following diagnosis was made: "Systemic lupus erythematosus, chronic course, with activity III, with the skin, blood vessels, liver, gastrointestinal tract, kidneys, nervous system, joints, and heart affected. Secondary antiphospholipid syndrome with damage to the central nervous system. Ischemic stroke in the territory supplied by the right middle cerebral artery. Mild dysarthria. Left hemiplegia." Multisystem lesion occurred in previous exacerbations of SLE, and this information was obtained from the patient's medical records. Pulse therapy was performed: solution of prednisone 1,000 mg No. 3 with subsequent switch to the tablet form of 60 mg per day, solution of cyclophosphamide 1,000 mg No. 1; antiplatelet therapy was prescribed including Cardiomagnyl 75 mg 1 tablet per day. During the stay of the patient in the Department: in neurological status without positive changes with preservation of left-sided hemiplegia. After 6 weeks, laboratory re-examination of blood — antibodies against phospholipids of 53.48 U/ml, antibodies against cardiolipin of 65.16 U/ml.

According to the 2012 American Rheumatology Association SLICC SLE, among central nervous system lesions, seizures and psychosis are included in SLE. At the same time, SLE with the ongoing secondary APS is much more often (in 20–30 % of cases) complicated by IS or transient cerebrovascular disease [1]. APS is a clinical and laboratory syndrome characterized by the formation of antibodies against own phospholipids in combination with autoimmune damage to systems and organs, most often in the form of venous and arterial thrombosis of any localization, obstetric pathology (intrauterine fetal death, miscarriage, abortion) and thrombocytopenia. The basis of occlusion in APS is non-inflammatory thrombotic vasculopathy. In addition, SLE and APS are actually risk factors for an earlier IS onset. This is due to additional risk factors that are typical for this pathology — immunopathological damage to blood vessels, persistence of immune complexes in the blood, specific drug therapy (glucocorticosteroids, hydroxychloroquine, cyclophosphamide). A number of studies have shown an earlier onset of cerebrovascular diseases in patients with SLE than in the control healthy group [2, 3]. There is also a tendency to recurrent IS, which took place in our patient a year later, in the territory supplied by the left middle cerebral artery with the formation of a focus in the parietal temporal lobe with the development of subtotal sensorimotor aphasia, despite the intake of

antiplatelets, anticoagulants and a maintenance dose of prednisolone.

Thus, the development of stroke in patients with SLE may be due to secondary APS and requires the assay of IgG ABs against phospholipids, lupus anticoagulant and determining the activity of the disease with the assay of antinuclear antibodies and antibodies to double-stranded DNA. For the prevention of cerebrovascular disease in SLE it is necessary to carry out the correction of risk factors (level of SLE activity, dyslipidemia, hypertension) to prevent thrombotic complications of oral anticoagulants and antiplatelet agents.

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DOI: 10.20514/2226-6704-2019-9-4-316-322 UDC 616.452-006.488-06:616.12-008.331.1

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CASE OF PHEOCHROMOCYTOMA WITH PERMANENT HYPERTENSION

Abstract

Pheochromocytoma is a tumor of chromaffin tissue that produces a large amount of biologically active substances (adrenaline, noradrenaline, dopamine), clinically manifested by hypertension and various metabolic disorders. Quite often the diagnosis is made only after autopsy. One of the reasons for late diagnosis is a great number of different clinical masks of the disease. Usually pheochromocytoma is suspected in patients with paroxysmal hypertension. We present a 37-year-old pregnant female (week 8 of pregnancy) with pheochromocytoma and permanent hypertension and sustained elevation of blood pressure up to 220/150 mm Hg. Her only complaint was vision disorder that started 3 months ago. Also, she noted a weight loss of 4 kg over the last 6 months. Retinopathy, left ventricle hypertrophy, tumor of right adrenal gland and glucose level disorders were revealed. Pregnancy was terminated for medical reasons. The patient took combination of doxazosin 0.4 mg, metoprolol 100 mg and moxonidin 0.4 mg per day and blood pressure was normalized to 130/90 mm Hg. Due to hypertension and tumor of right adrenal gland that are accompanied by retinopathy and metabolic disorders, pheochromocytoma was suspected. Contrast-enhanced computed tomography confirmed the tumor (60×73×70 mm) of right adrenal gland. Urinary normetanephrine level was 5.5 times higher than the norm. Magnetic resonance angiography of cerebral vessels was done because of malignant hypertension and family history (the patient's sister had died of cerebral hemorrhage). Fusiform aneurysm of right internal carotid artery was revealed. The patient underwent laparoscopic resection of right adrenal gland. Histologic examination: pronounced cellular and nuclear polymorphism, invasion of tumor cells into a fibrous capsule, which does not exclude the malignant nature of pheochromocytoma. Follow-up period lasted for 8 months and was characterized by normalization of blood pressure, glucose level and weight gain of 3.5 kg. Computed tomography of retroperitoneal space and normal urinary metanephrine tests revealed no recurrent pheochromocytoma.

Key words: *pheochromocytoma, hypertension*

Conflict of interests

The authors declare no conflict of interests

Source of financing

The authors states that no finding for the study has been received

Article received on 03.04.2019

Accepted for publication on 19.06.2019

For citation: Yakovleva E. V., Lobanova O. S., Zhukova E. V. et al. CASE OF PHEOCHROMOCYTOMA WITH PERMANENT HYPERTENSION. The Russian Archives of Internal Medicine. 2019; 9(4): 316-322. [In Russian]. DOI: 10.20514/2226-6704-2019-9-4-316-322

BP — blood pressure, DBP — diastolic blood pressure, SBP — systolic blood pressure, ECG — electrocardiogram

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Pheochromocytoma is a tumor of chromaffin tissue that produces a large amount of biologically active substances (adrenaline, noradrenaline, dopamine), clinically manifested by hypertension of varying severity and various metabolic disorders. The prevalence of pheochromocytoma among patients with hypertension does not exceed 1 %, the peak incidence is in the age of 30–50 years [1, 2]. In one third of patients with chromaffin tumors the cause of the disease is hereditary mutation [1, 5]. The diagnosis of pheochromocytoma is often established post mortem [1, 3]. At the same time, patients with pheochromocytoma belong to the rare category of patients with hypertension, in whom timely diagnosis and provision of effective medical care can contribute to recovery. One of the main reasons for the late diagnosis of chromaffin tumors is the variety of clinical masks of the disease [3]. The combination of symptoms and their severity even in one patient can vary significantly. We followed-up a female patient with pheochromocytoma, who may have had no symptoms of increased BP, but had only bradycardia with ventricular bigeminy or ventricular paroxysmal tachycardia with episodes of ventricular fibrillation or had a developing crisis with vivid manifestations in the form of muscle tremors, profuse sweat, fear of death, feelings of suffocation, nausea and vomiting at the same degree of BP increase [4]. Among the causes of underdiagnosis lack of awareness of doctors about the various manifestations of the disease should be noted. In clinical practice, a targeted search for pheochromocytoma is carried out mainly in the presence of paroxysmal hypertension. However, in chromaffin tumors, a course with permanent hypertension is possible [3]. The idea of the possibility of low-symptomatic adrenal tumors has expanded in recent decades, due to the active introduction of imaging techniques into practice. According to the latest data, in 4–5 % of patients exposed to radiological imaging adrenal incidentaloma (from the English word «incidental») — a mass formation larger than 1 cm in diameter detected by accident and requiring nosological specification — was revealed [5]. Approximately 5 % of patients with adrenal incidentaloma were diagnosed with pheochromocytoma [2]. With all the improvement and increase in the availability of instrumental methods of examination, the timeliness of the beginning of the diagnostic search for chromaffin tumors when patients turn to primary care doctors remains relevant. In this regard, the clinical case of a female patient with pheochromocytoma with permanent hypertension, identified when visiting a doctor for another reason, is of interest.

Patient K., 37 y.o., visited maternity welfare clinic at gestational age of 8 weeks. During the initial examination, an increase in BP to 220 and 150 mm Hg was reported, which was the reason for hospitalization in Cardiology Department of Saratov Regional Clinical Hospital. When collecting medical history, it was found that the main complaint of the patient was deterioration of vision during the last 3 months. Also, the patient noticed a decrease in body weight by 4 kg for six months, which she did not consider as important. This is the third pregnancy, during the previous two pregnancies at the age of 20 and 28 years BP did not increase. Delivery was performed by caesarean section according to obstetric indications (contracted pelvis). During the annual preventive medical examination (worked as a teacher in kindergarten), the BP level increase was not observed. The last measurement of BP was performed a year ago. Clarification of data on hereditary diseases was difficult, since there is no information about the parents; the patient grew up and was brought up in a foster home from the age of five. It is known that her sister died suddenly at the age of 37 years from a cerebral hemorrhage. She denies the use of alcohol, drugs. She smoked from 29 to 36 years. On examination, the condition was relatively satisfactory. Height 147 cm, weight 50 kg, body mass index 23.14 kg/m^2. The skin is clean, of normal color and moisture. Musculoskeletal system — without pathology. Apex beat is palpated in the 5th intercostal space along the left mid-clavicular line, coincides with the left border of relative cardiac dullness. Heart sounds are rhythmic and clear. Heart rate was 82 per minute. BP on the right hand was 220 and 130 mm Hg, BP on the left hand was 210 and 125 mm Hg. Examination of respiratory, gastrointestinal, urinary, nervous system revealed no pathology. The thyroid gland at palpation had soft and elastic consistency, and it was not increased, nodular formations are not

palpated. Upon admission, the patient was prescribed methyldopa 1,000 mg followed by an increase in the daily dose to 2,000 mg per day and metoprolol 50 mg per day. On the third day, BP decreased to 150 and 90 mm Hg.

In blood count hemoglobin was 134 g/l, red blood cells — 4.24×10^{12} g/l, white blood cells — 9.9×10^{9} g/l, platelets — 293×10^{9} g/l, increased erythrocyte sedimentation rate up to 30 mm per hour. Blood chemistry showed an increase in fasting blood glucose up to 6.4 mmol/l, glycated hemoglobin — up to 6.0 %, cholesterol — up to 6.0 mmol/l, C-reactive protein — up to 30 mg/l. The content of serum creatinine, urea, electrolytes, total protein, albumin, bilirubin, aspartate aminotransferase and alanine aminotransferase activity are within normal values. In urinalysis proteinuria of 0.15 g/l was revealed. Daily proteinuria was 1.57 g/l, and it was not revealed in re-examination. In ECG sinus rhythm was reported with heart rate of 67 bpm, and normal semihorizontal electrical axis. According to the echocardiographic dimensions of the heart chambers, the global contractility of the left ventricular myocardium is within normal limits, EF was 59.8 % by Simpson. Concentric left ventricular hypertrophy: myocardial mass of 142 g, the index of myocardial mass of left ventricle 142 g/m^2, the thickness of the left ventricle posterior wall of 1.23 cm, the interventricular septum of 1.14 cm. Diastolic function of the left ventricle impaired with relaxation type, there are false chords in the apical region of the left ventricle. The results of daily monitoring of blood pressure revealed a change in the daily BP profile of "non-dipper" type, increased variability of SBP. In the daytime, the average SBP was 221 mm Hg, average DBP — 132 mm Hg; at night the average SBP — 234 mm Hg, average DBP — 135 mm Hg. Ultrasound examination of the thyroid gland revealed no pathology. Data on abdominal and renal ultrasound: deformation of the gallbladder; position, size, echogenicity of the kidneys are within normal limits. In the projection of the right adrenal gland there was a formation of increased echogenicity measuring 63×52 mm. In the duplex study of renal arteries, hemodynamically significant blood flow disorders in the common renal arteries were not revealed, resistance indices were normal. Ophthalmologist diagnosed neuroretinopathy of both eyes, reduced visual acuity in both eyes to 0.8. Upon re-examination after 4 days, a negative change was noted: reduced visual acuity in the right eye — to 0.7, left eye — to 0.6; increase in the number of stroke-like hemorrhages, plasmorhagia, exudates in the macula, increase in the number of newly formed vessels in the optic disc.

Taking into account the 3rd stage of hypertension with the development of rapidly progressed retinopathy and left ventricular hypertrophy, and the formation of the right adrenal gland, the patient was offered an abortion for medical reasons by the decision of the multidisciplinary team meeting. Instrumental curettage of the uterine cavity was performed at 8 weeks of gestation. After the abortion, the patient assessed her state of health as satisfactory, the only complaint was a decrease in vision. The presence of malignant hypertension and adrenal gland formation, accompanied by metabolic disorders, determined the need for priority search for pheochromocytoma. With this in mind, antihypertensive therapy was changed: methyldopa (the drug is contraindicated in pheochromocytoma) was discontinued, doxazosin 0.4 mg, metoprolol 100 mg, moxonidin 0.4 mg per day were prescribed. Combined antihypertensive therapy allowed to maintain the SBP within 125–135 mm Hg, DBP — 90–95 mm Hg. The orthostatic test showed a positive result: in the transition from horizontal to vertical position SBP decreased by 20 mm Hg. On the first day after the abortion in the absence of coronary and heart failure symptoms on ECG in the leads from V_2 to V_6 the appearance of symmetrical negative T-waves was reported (Fig. 1).

Test for blood troponins did not reveal excess of normal values. According to repeatedly performed echocardiographic studies no negative change was observed.

After curettage of uterine cavity, there was a decrease in RBC to 3.74×10^{12} g/l, hemoglobin to 97 g/l, thrombocytosis 485×10^{9} g/l, ESR 40 mm/h. During the week after the abortion, the blood WBC remained within normal values, then a short-term leukocytosis of 18×10^{9} g/l appeared twice in the absence of signs of any infectious process. The data from blood chemistry: cholesterol of 6.0 mmol/l, low density lipoprotein cholesterol

of 4.2 mmol/l, blood glucose of 10.6 mmol/l, potassium of 4.19 mol/l, sodium of 142 mmol/l, creatinine of 74.3 mmol/l, C-reactive protein of 39.5 mg/l. Glycemic profile: 08.00 — 5.6 mmol/l, 13.00 — 14.9 mmol/l, 18.00 — 11.6 mmol/l, 22.00 — 11.2 mmol/l. In urine tests, transient glucosuria, microalbuminuria were noted.

Hormonal status study: cortisol at 08.00 — 556 nmol/l (norm of 138–690 nmol/l), at 18.00 — 150 nmol/l (norm of 69–345 nmol/l); thyroid stimulating hormone — 2.1 IU/ml, free triiodothyronine — 3.0 pmol/l, free thyroxine — 10 nmol/l, antibodies against thyroid peroxidase — 66 IU/ml. The study of urine metanephrine and normetanephrine was performed by high-performance liquid chromatography. Analysis results: total metanephrine 23 μg/day (norm of <320 μg/day), free metanephrine 90 μg/day (norm of 1.6–192 μg/day), total normetanephrine 2,148.0 μg/day (norm of <390 μg/day), free normetanephrine 111 μg/day (norm of 7–158 μg/day). Thus, the content of total normetanephrine exceeded normal values by 5.5 times, which confirmed the presence of chromaffin tumor.

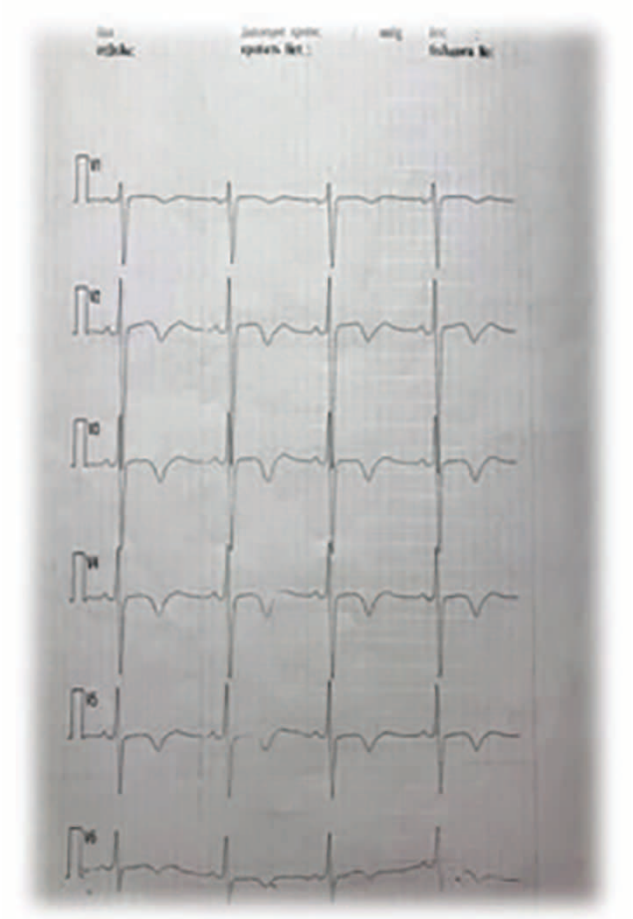

Figure 1. *Catecholamine-induced cardiomyopathy. ECG chest leads symmetric negative T-wave*

For the purpose of topical diagnosis of the proposed tumor, computed tomography of the abdominal cavity and retroperitoneal space was performed. In the right adrenal gland, a pathological soft tissue formation with dimensions of 57×72×74 mm with uneven contours, an inhomogeneous structure, without a clear border with the right lobe of the liver, the right kidney, the lower vena cava was found. The left adrenal gland is normal. To determine the surgical strategy of patient's treatment an additional study with contrast enhancement using Scanlux was performed. The following results are obtained: in the right adrenal gland, a formation measuring 60×73×70 mm with a round shape and clear smooth contours was revealed, its structure is heterogeneous due to the presence of a centrally located area of reduced density. With the administration of a contrast agent, the accumulation of contrast in the arterial phase along the periphery in the form of lumps was noted, in the central part contrast accumulation was not observed. The formation closely adheres to the liver, right kidney, inferior vena cava without growth into the adjacent organs. The renal hilum of the right kidney is pushed down by the formation. Lymph nodes of the abdominal cavity and retroperitoneal space, pelvic cavity are not enlarged. Taking into account the malignant course of hypertension and a positive family history, magnetic resonance angiography of brain vessels is included in the examination plan. On a series of angiograms performed in the ToF mode (time-of-flight magnetic resonance angiography), an uneven expansion of the lumen of the right internal carotid artery to 7.8 mm at the level of C3–C4 segments is determined, indicating the presence of a fusiform (spindle-shaped) aneurysm of the petrous segment of the right internal carotid artery.

<u>Preoperative clinical diagnosis:</u>

Primary disease: Pheochromocytoma (formation of the right adrenal gland). Secondary hypertension. Left ventricular hypertrophy. Catecholamine-induced cardiomyopathy. Hypertensive neuroretinopathy. Fusiform aneurysm of petrous segment

of the right internal carotid artery. Impaired fasting glucose. Dyslipidemia. Condition after instrumental curettage of the uterus at 8 weeks of gestation. Uterine scar.

Concomitant disease: Connective tissue dysplasia syndrome: false chords in the apical region of the left ventricle. Deformation of the gallbladder. Mild chronic normochromic anemia. Secondary thrombocytosis.

The patient underwent laparoscopic adrenalectomy on the right with technical difficulties in isolating the right adrenal vein. The removed right adrenal gland is 8×7×7 cm in size, and the section revealed a tumor of 7.0 cm in size, typical of a variegated pheochromocytoma with multiple foci of hemorrhage (Fig. 2).

Histologic examination: solid alveolar complexes consisting of large polygonal cells with pronounced cellular and nuclear polymorphism, surrounded by a fibrous capsule, with invasion of tumor cells into this capsule (Fig. 3, 4).

The early postoperative period was complicated by acute adrenal insufficiency, which required intravenous administration of prednisolone 180 mg, hydrocortisone 400 mg on the first day. In the next two days, hydrocortisone was intramuscularly administered at a dose of 175 mg per day. On the fourth day there was a normalization of BP and carbohydrate metabolism parameters. In the postoperative period ECG revealed no negative changes, blood troponins did not increase, electrolytes were within normal values. The patient was discharged in a satisfactory condition on the tenth day after surgery. After the rehabilitation period, the patient returned to work.

Eight months after the right-sided adrenalectomy, the patient was hospitalized in Endocrinology Department of Saratov Regional Clinical Hospital. She assessed her health as good, she had no complaints and noted a weight gain of 3.5 kg. Blood count and urinalysis was normal. Blood glucose — 5.4 mmol/l, glycated hemoglobin — 5.2 %, increased total cholesterol to 6.2 mmol/l; other blood chemistry parameters are normal. BP at home and office measurement did not exceed 120 and 80 mm Hg. According to the daily monitoring of blood pressure, there was a slight increase in the mean value of SBP at night (122 mm Hg), the daily profile of BP is changed by "non-dipper"

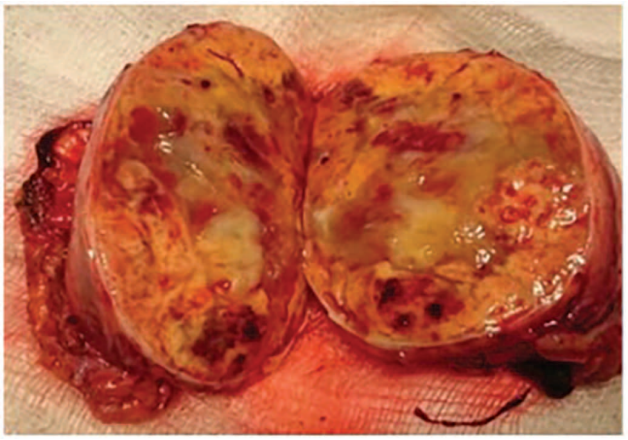

Figure 2. *Tumor 7 cm in diameter of specific for pheochromocytoma gray cherry color with multiple foci of hemorrhage in the section of the removed adrenal gland*

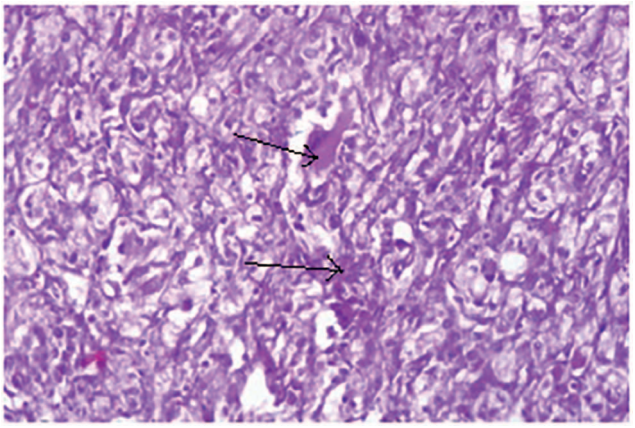

Figure 3. *Histological pattern of adrenal gland formation (hematoxylin and eosin). Large polygonal cells with pronounced cellular and nuclear polymorphism*

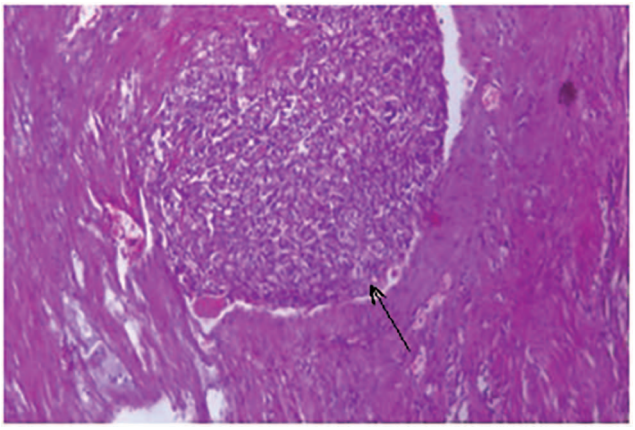

Figure 4. *Histological pattern of adrenal gland formation (hematoxylin and eosin). Invasion of tumor cells in the fibrous capsule*

type. Computed tomography of the retroperitoneal space was performed, evidence of recurrent pheochromocytoma was not found. Visual acuity of the right eye was 0.8, of the left eye — 0.9. The optic disc is pale pink with clear boundaries; the arteries are tortuous, narrowed; the veins are dilated, the macula has dystrophic foci. On ECG there was a positive change, but without full recovery of repolarization processes (Fig. 5).

Urine content of metanephrines was within normal values: total metanephrine of 48.00 μg/day, free metanephrine of 5.75 μg/day, total normetanephrine of 131.0 μg/day, free normetanephrine of 15.4 μg/day. Blood cortisol at 8.00 — 454 nmol/l, at 18.00 — 95 nmol/l.

Thus, in the presented clinical case of pheochromocytoma, hypertension was characterized by resistance and absence of crises. Weight loss should be noted as the earliest manifestation of the disease. Pregnancy in the patient occurred on the background of the existing tumor, since the first symptoms (decreased vision and weight loss) were already present in the early stages of the pregnancy. Of the organ lesions, the most severe was retinopathy, the rapid progression of which corresponded to the malignant course of hypertension. The formation of a fusiform aneurysm of the internal carotid artery is regarded as a consequence of persistent systolic-diastolic hypertension, possibly secondary to connective tissue dysplasia. Catecholamine-induced cardiomyopathy, diagnosed according to the appearance of myocardial focal changes on ECG in the anterior-septal-apical-lateral region of the left ventricle was not accompanied by clinical signs. Its development in pheochromocytoma is associated with catecholamine-induced non-coronary myocardial necrosis, leading to disruption of intercellular and intracellular ion exchange and oxidative intracellular cycle [3]. The metabolic disorders diagnosed in the patient are quite typical for chromaffin tumors. In 10–40 % of patients with chromaffin tumors there is impaired glucose tolerance and paroxysmal hyperglycemia during a hypertensive attack, in 10–29 % of patients — diabetes mellitus [3]. Leukocytosis and thrombocytosis in patients with chromaffin tumors are due to the shrinkage of the spleen under the influence of catecholamines. In the presented case, as in the previous one, leukocytosis reached a significant degree of severity — 18×10^9 g/l [4].

Histological features of the tumor, namely the presence of severe cellular and nuclear polymorphism, invasion of tumor cells in the fibrous capsule, do not exclude the malignant nature of pheochromocytoma. However, it should be noted that the question on the criteria for malignancy of pheochromocyte has not yet been resolved and is debatable. The discussion is based on the fact that in pheochromocytoma there is a discrepancy between the morphologically benign nature of the primary tumor and the subsequent metastatic lesion. On the other hand, when using the criteria of nuclear and cellular polymorphism, atypia and the presence of vascular and capsular invasion, the incidence of malignant lesions is 35–65 %, but clinically aggressive course is practically not found [1].

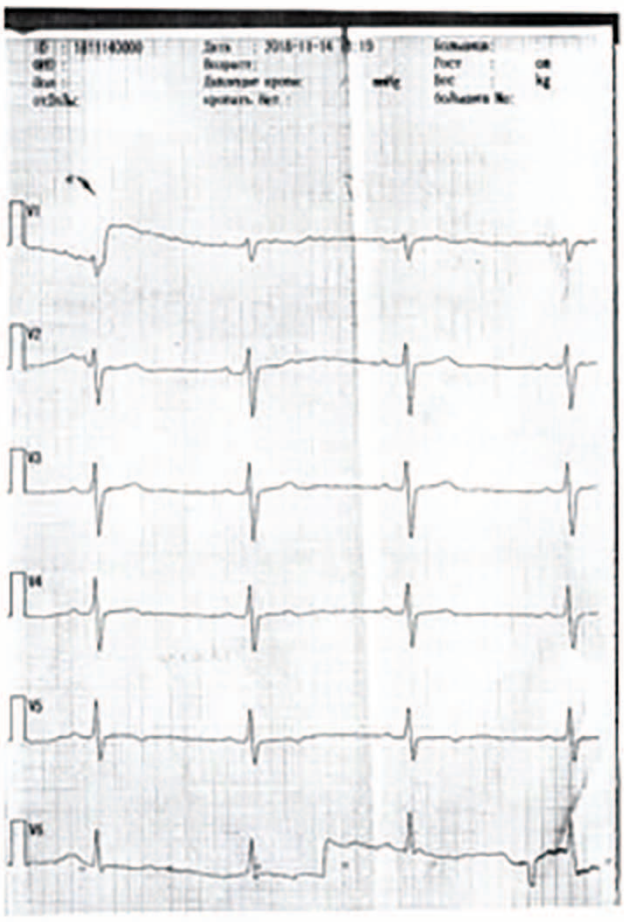

Figure 5. *ECG recorded 8 months later after adrenalectomy. Disorders in repolarization processes in the myocardium: the T-wave is low-amplitude in the thoracic leads and weakly negative in V5 lead*

It is possible that the sudden death of the sister at the age of 37 years from a cerebral hemorrhage was associated with pheochromocytoma and the disease has a family history. In this case, the probability of recurrent pheochromocytoma increases, which necessitates further careful monitoring of the patient. We believe that in this case the combination of circumstances allows us to hope for a favorable outcome. If there was no reason to see a doctor because of her pregnancy, the situation could have developed unfavorably, since in the presence of malignant hypertension and formed aneurysm of the internal carotid artery, the development of fatal cardiovascular events in the short-term was very likely.

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