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VON HIPPEL-LINDAU SYNDROME: ASPECTS OF TREATMENT AND MANAGEMENT. CASE REPORT AND LITERATURE REVIEW

Abstract

The steadily growing interest in studying of endocrine genetics is driven not only by the search for new pathologies but also by the most pressing need to develop methods for early diagnosis, treatment and management of such patients. Though 20 % of all the patients with von Hippel-Lindau syndrome do not have a family history of the disease, a genetic basis is a natural characteristic of the disease and it determinates a phenotype. Despite the non-aggressive course, in general, a relative unpredictability of the syndrome signs onset and the lack of regular monitoring can increase the risk of surgery complications and cause a disability at a young age. The presented clinical case shows the need for a multidisciplinary approach to management of the patients with von Hippel-Lindau syndrome.

Key words: *phacomatosis, Von Hippel-Lindau syndrome, pheochromocytoma, hemangioblastoma, VHL*

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Anti-VEGF — anti-vascular endothelial growth factor; VHL syndrome, VHL — von Hippel-Lindau syndrome; CT-computed tomography; MIBG — 123I-MIBG, metaiodobenzylguanidine; MRI —magnetic resonance imaging; RCC — renal cell carcinoma; PET — positron emission tomography; RPM — radiopharmaceutical; US — ultrasound; NMRCE — Federal State Budgetary Institution of National Medical Research Center of Endocrinology of Ministry of Health of Russia; CNS — central nervous system

Relevance

Von Hippel-Lindau syndrome is a phacomatosis with an autosomal dominant inheritance type, manifested by the formation of angiomatous, angioreticulomatous and cystic formations of the retina, central nervous system and internal organs. At the heart of the pathogenesis is a mutation in the 3p25-26 site, where the tumor suppressor gene VHL is localized. The product of the mutated gene leads to overregulation of genes inducing systemic hypoxia, accelerating angiogenesis, initiating abnormal capillary growth and the formation of multisystem tumors with benign and, less often, malignant potential [1]. Depending on the clinical manifestations within the VHL syndrome, two phenotypes are distinguished: type 1 occurs without pheochromocytoma, includes angiomas (vascular tumors) of the retina, CNS hemangioblastoma (central nervous system), renal cell carcinoma (RCC), pancreatic, renal and splenic cysts, solid pancreatic tumors,

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rarely — adenocarcinomas, cystadenomas of the epididymus and endolymphatic sac tumor; type 2 — with pheochromocytoma, is divided into subtypes: 2A — with a low risk of kidney cancer, 2B — with a high risk of kidney cancer, 2C is represented only by pheochromocytoma [2–4]. Due to the success of genetic testing, verification of mutations has become available, resulting in timely diagnosis and medical intervention, preventing disability and death at a young age from VHL syndrome. However, the subsequent management of the patient requires a multidisciplinary approach in order to actively monitor the components of the disease and identify „sleeping" tumors, potentially having an aggressive resource (metastasis, compression syndrome). In this article, we describe the clinical case of a patient with von Hippel-Lindau syndrome type 2, demonstrating the complexity of dynamic management of the patient with this pathology, despite the classical pattern of evolution of its components.

Description of the clinical case

Patient B., 25 years old, first admitted to Department of Therapeutic Endocrinology of NMRCE of Ministry of Health of Russia in May, 2017, with complaints of heart pain, palpitations, weakness, nausea, vomiting, decreased appetite up to aversion to food, sleep deterioration. It is known from medical history that since 2005 (from the age of 14 years) the patient noted an episodic increase in blood pressure to 160/100 mm Hg., palpitations, and this was the reason for his hospitalization in the Department of Pediatric Endocrinology of Endocrinology Center of RAMS in 2006, which was meant to exclude the endocrine cause of hypertension. Upon questioning the patient and relatives it found that his grandmother (father's mother) in 1968 (at the age of 24 years) was diagnosed with bilateral adrenal pheochromocytoma with metastasis (for which radiotherapy was carried out without a positive effect, surgical treatment), in 1984 — paraplegia of the lower extremities (MRI — multiple formations of the spinal cord). In 1996, the patient's father underwent surgery for bilateral adrenal pheochromocytoma, and in 2005 with the appearance of neurological symptoms (pain, paresthesia) in the lower extremities, further examination revealed hemangioblastomas of the spinal cord (subsequently manifesting with development of persistent tetraparesis), according to a genetic study — a mutation of *Trp157Ile* in exon 3 of the *VHL* gene. Taking into account positive hereditary epy history with successive manifestations of multiple tumor growth and cardiovascular events, the nucleotide sequence of exon 3 of the *VHL* gene was analyzed for genetic verification of the disease by polymerase chain reaction and subsequent sequencing by Sanger: a heterozygous mutation of *Trp157Ile* in exon 3 gene was revealed, confirming the presence of the above-mentioned syndrome in the patient. Along with this, according to the results of a comprehensive examination, the formation of the right adrenal gland measuring 1.5×1.4×1.1 cm was diagnosed, with a noradrenaline type of secretion, which is a predominantly characteristic of the von Hippel-Lindau syndrome: increased normetanephrine — 673 μg/day (normal range of 35–445 μg/day), with normal levels of metanephrine 167 μg/day (normal range of 25–312 μg/day). To exclude the extra-renal location of the paraganglioma, a scintigraphy with 123 I-MIBG was performed. As a result, the focus of abnormal accumulation of RPM was observed only in the right suprarenal region. With ultrasound, MRI of the abdominal cavity and kidneys, as well as scintigraphy, the left adrenal gland was intact. Ophthalmological examination revealed: angiomatous node in the lower-outer quadrant of the retina of the left eye — angiomatous node in the lower-outer quadrant and the area of the equator of the retina in the right eye, in connection with which the patient had a session of laser photocoagulation. Brain MRI data are not represented. Thus, based on the clinical picture, the results of genetic and laboratory and instrumental studies, the final clinical diagnosis was articulated as follows: von Hippel-Lindau syndrome. Pheochromocytoma of the right adrenal gland. Hemangiomas of the retina in both eyes. After preoperative preparation with doxazosin at a dose of 8 mg/day to achieve stable hemodynamic parameters (BP within 120/70–80 mm Hg.) 08.04.2007 right-hand laparoscopic

adrenalectomy with a tumor was performed in the Surgical Department of NMRCE without development of adrenal insufficiency afterwards. After discharge, the patient continued to be followed-up in the Clinic of Eye Microsurgery n.a. S.N. Fedorov, where he repeatedly underwent laser photocoagulation of the retina for newly formed hemangioblastoma (no subjective deterioration of vision). In 2008 during the MRI of the brain and spinal cord focal masses of the cerebellum, cervical, thoracic spinal cord were revealed, and this was his reason for 2 sessions of CyberKnife in Germany in 2008 and 2013. Since 2014, for the first time the patient noticed episodes of palpitations, increased sweating. During abdominal MRI it was revealed the mass of the left adrenal gland measuring 2.7×2.3×2.5 cm with characteristic for pheochromocytoma hyperintensive signal on T2-weighted images (in relation to adrenal tissue); hormonal study confirmed hypersecretion of methylated catecholamines in daily urine, and therefore in April 2015 in the Surgical Department the patient underwent left-sided adrenalectomy. A histological study of adrenal preparations from 2007 and 2015 revealed a similar pattern: tissue of the adrenal glands with nodular hyperplasia and rearrangement of the cortical layer. A tumor of large polymorphic cells with hyperchromic nuclei and nuclear inclusions with mixed growth pattern was found in the adrenal medulla: alveolar, forming mainly large nests, turning into diffuse, without signs of penetration of the capsule. In the central parts of the tumor hemorrhages were determined (Fig. 1–3).

Immunohistochemistry on sections from paraffin blocks was performed automatically in Bond max Leica immunostainer with antibodies to chromogranin A, synaptophysin, S100, Ki-67. The results confirmed a diffuse positive reaction with antibodies to chromogranin A and synaptophysin (Fig. 4), which proves the neuroendocrine nature of masses; negative reaction with markers of the adrenal cortical layer: proteins melan A and alpha-inhibin; positive reaction with antibodies to S-100 was noted (Fig. 5), however, the proliferation index Ki-67 was less than 1 %, which in total directly indicates the low malignant potential of both tumors.

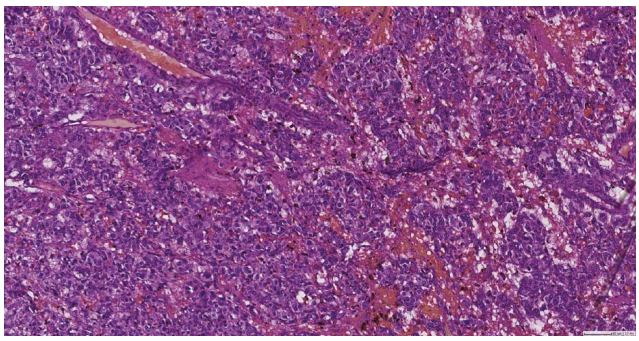

Figure 1. *Pheochromocytoma of the right adrenal gland. Stained with hematoxilin and eosin. Magnification 100×*

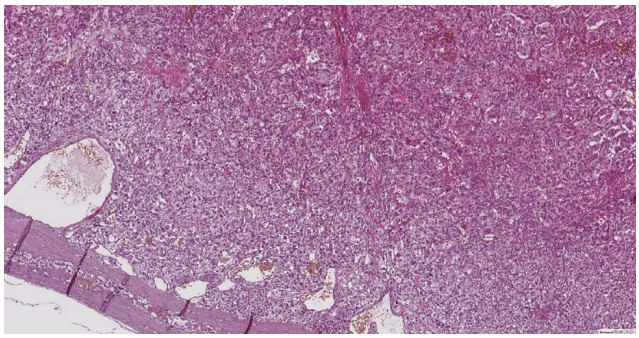

Figure 2. *Pheochromocytoma of the left adrenal gland. Stained with hematoxilin and eosin. Magnification 100×*

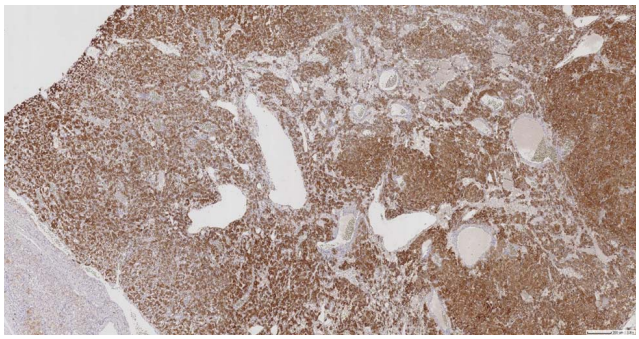

Figure 3. *Positive reaction of tumor cells with synaptophysin. Magnification 100×*

In the postoperative period, replacement therapy of adrenal insufficiency with hydrocortisone 60 mg/day was prescribed. After discharge, at the place of residence, the patient independently adjusted the dose of the drug, without consulting a doctor. Since November 2016, the relapse of heart attacks and sweating, persisting despite an increase in the dose of hydrocortisone, occurred. Since April 2017, heart pain of compressive nature began,

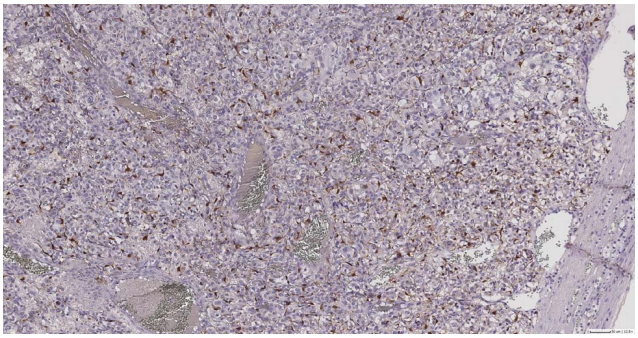

Figure 4. *Positive reaction of sustentacular cells with anti-S100 antibodies. Magnification 100×*

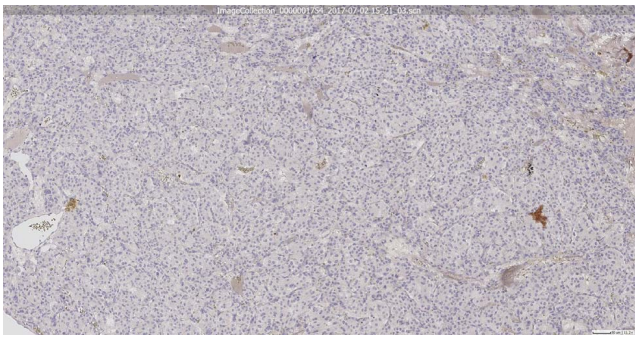

Figure 5. *No reaction with antibodies against the Ki-67 protein (cellular marker for proliferation). Magnification 100×*

which was the reason for cardiologist to prescribe at the place of residence potassium + magnesium asparaginate 4 tablets per day, and the patient subjectively noted a positive change in the form of pain relief. In May 2017, the patient had an outpatient appointment at NMRCE with complaints of heart pain, severe weakness, nausea, vomiting, aversion to food, heartbeat up to 130/minute while taking 60 mg of hydrocortisone per day. Summarizing the clinical manifestations and the data of the presented analyses (hyperkalemia up to 5.2 mmol/l (3.5-5.1), hyponatremia 134 mmol/l (136–145)), the patient's condition was regarded as a pronounced decompensation of adrenal insufficiency, in connection with which he was hospitalized in the Department of Therapeutic Endocrinology. Upon examination, the patient's height and weight were 184 cm and 82 kg respectively; there were obvious clinical signs of adrenal insufficiency: severe weakness, nausea, blood pressure reduced to 90/60 mm Hg, tachycardia 100 bpm, positive changes in well-being with the injection of hydrocortisone 100 mg in the injectable form. Given a history of bilateral adrenalectomy, a typical water-electrolyte imbalance (hyperkalemia in combination with hyponatremia), an increase in renin of more than 500 μm/ml (2.8–39.9) and a decrease in aldosterone to 26.9 pmol/l (54.5–57.0), the patient's condition was regarded as severe, caused by mineralocorticoid insufficiency. During treatment with fludrocortisone 0.1 mg with adjustment of hydrocortisone dose to 30 mg/day, a state of compensation for primary adrenal insufficiency was achieved. Taking into account the genetically confirmed von Hippel-Lindau syndrome, a further examination plan was drawn up with an emphasis on the dynamic control of the „target organs". Levels of catecholamine metabolites remained within normal limits in daily urine: normetanephrine 435.42 μg/day with normal range of up to 445 and metanephrine 82.08 μg/day with normal range of up to 312. However, taking into account the history of metastatic pheochromocytoma in the grandmother, the state after bilateral adrenalectomy, the level of normetanephrine at the upper normal level is regarded as suspicious with respect to the probable non-adrenal localization of paragangliomas and metastases. Despite the rare occurrence of non-adrenal localization of pheochromocytoma in *VHL* syndrome and the results of histological studies, scintigraphy with 123 I-MIBG was performed: there is no evidence of relapse. In abdominal and renal US no focal pathology was found, urological examination revealed right testicular cysts and cysts of left epididymis. In the ocular fundus no new hemangiomas were revealed, the old ones were completely desolated during treatment. In MRI of the brain and spinal cord — mass in the left hemisphere of the cerebellum, intramedullary masses of the cervical spine without growth changes; moderate negative changes were found: at the level of Th 6-7, mass measuring 6×5mm, with perifocal edema for 3 cm — which, according to the neurosurgeon's consultation, required MRI monitoring after 6 months. As a result of hospitalization in 2017, the patient was discharged in a satisfactory condition with recommendations for treatment and an outpatient follow-up plan The patient was subsequently admitted in the Department again a year later with complaints of episodic

attacks of palpitations. Taking into account the increased risk of tumors from chromaffin tissue, in the first place, the recurrence of paraganglioma was excluded during the examination: in daily urine: normetanephrine — 531.13 μg/day (up to 445), methanephrine 64.532 μg/day — (up to 312). The status of ocular fundus according to ophthalmoscopy remained stable: the field of view on the white color was unchanged, no new hemangiomas were diagnosed. The examination of the pancreas showed no evidence of the presence of masses. With ultrasound of the scrotum, cysts of both epididymis persist — on the right side up to 17 mm, on the left side — up to 5 mm — without significant change compared to May 2017. Negative change was verified by MRI of the spinal cord and brain in comparison with 2017: at the level of Th 6-7, the mass has size of 9×6 mm with perifocal edema with length of 6 cm (in May 2017 — dimensions 6×5mm, with perifocal edema over 3 cm); at the level of Th12-L1, three masses located at a short distance from each other with dimensions of 6 mm, 5 mm and 3 mm, with moderately pronounced perifocal edema (in May 2017 — at the level of Th12, masses with dimensions of 5 mm, 3 mm and 2 mm, respectively, with moderate perifocal edema); in the left hemisphere of the cerebellum there is a focus with a diameter of 5 mm, with an ambient area hyperintensive to flair and T2-weighted images measuring 8×19 mm (in May 2017 — a focus with a diameter of 4 mm, with an ambient area hyperintensive to flair and T2-weighted images of size 10×19 mm), a new focus up to 2 mm in the left parietal lobe, intensively accumulating contrast drug, with peripheral edema. Given the progression of MRI, according to the recommendations of the neurosurgeon at the center, the patient was referred to NMRC of Neurosurgery n.a. N.N. Burdenko to consider an option of radiosurgical treatment. The concomitant clinical problem in this episode was the newly revealed right kidney mass measuring 3.8×3.9 cm according to renal US, and during further examination by MRI of retroperitoneal space there was the pattern of cystic solid tumor measuring 44×42×46 mm in the lower pole of the right kidney with signs of hemorrhage (Bosniak II) in the presence of intact layers of paranephric fat tissue. Due to the fact that PCC in 30 % of cases is part of the phenotypic manifestations of *VHL* syndrome and is the main cause of death in mutant gene carriers, the patient consulted an oncourologist. According to the expert opinion, this type of Bosniak cyst has a malignant potential with a probability of no more than 20 %, and therefore it was recommended to continue monitoring with a repeat of CT after 6 months.

Discussion

Genetically programmed formation of benign and malignant tumors in carriers of *VHL* gene mutation throughout life allows us to note that the difficulties in monitoring this cohort of patients are mainly due to the polysystemic lesions involving the central nervous system, visceral organs such as kidneys, pancreas, adrenal glands, and reproductive system organs, as well as the need for strict dynamic monitoring of the predicted manifestation of „silent“ tumors with wide range of localization. Pheochromocytoma may be the debut of *VHL* syndrome, especially in childhood. In 70 % of cases it is a benign mass of adrenal localization, in 50 % of cases it has bilateral localization with exclusively noradrenaline type of secretion [5]. Non-adrenal paragangliomas in *VHL* syndrome occur in 30 % of cases [2]. A feature of the biochemical phenotype of such tumors is a more pronounced expression of tyrosine kinase, inducing higher concentrations of continuously secreted catecholamines. Diagnosis is carried out using MRI, CT with contrast enhancement, PET with 6-18F- fluorodopamine, ^{123}I MIBG — scintigraphy. Although ^{123}I MIBG scintigraphy is the „gold standard“ among all functional methods for pheochromocytoma imaging, in *VHL* the relative lack of storage granules or reduced expression of membrane norepinephrine and vesicular monoamine transporters can lead to a false negative result. The primary method of treatment is surgical, subject to mandatory preoperative preparation with alpha-blockers [6]. In 60–80 % of patients, clinical manifestations of von Hippel-Lindau syndrome are largely due to the occurrence of hemangioblastomas in the central nervous system — benign tumors of blood vessels. The primary diagnostic method is the MRI of the brain and spine with contrast enhancement.

In the nervous tissue, the growth of the tumor, surrounded by a thin shell, provokes the development of compression syndrome with exudation into the surrounding structures. Craniospinal localization of the lesion is subject to surgical treatment, but since CNS hemangioblastomas are characterized by chaotic growth, it is not used until the appearance of clinical symptoms. Stereotactic radiosurgery is used to treat small CNS tumors (less than 3 cm in diameter), as well as in in inoperable cases [7, 8]. For verification of retinal hemangioblastoma regular examination of the ocular fundus is required, as in 5–8 % of patients their development leads to blindness and severe visual impairment. The primary method of treatment is immediate laser coagulation or cryotherapy (the most effective for tumors with a diameter of less than 3 mm); vitreoretinal surgery is used in cases of retinal detachment. Tumors located near the optic nerve are subject to anti-VEFG therapy, which helps to reduce edema and exudate formation [9, 10]. In *VHL*-syndrome type 1 or 2B formation of benign liver cysts, kidney cysts or RCC, which is manifested in 45 % of patients, characterized by asymptomatic course and diagnosed using CT, is observed. And in 60 % of patients with *VHL* by the age of 60 years, PCC manifests and it is the main cause of death in this group of patients. Metastasis correlates with size of the mass, therefore surgical treatment is indicated in tumors larger than 3 cm (US standard) /5 cm (European standard) [5, 11]. Gold standard of PCC treatment — organ-preserving surgery: open and laparoscopic partial nephrectomy. Currently, the most promising alternative methods are cryotherapy and radiofrequency ablation [3, 11]. 12–77% of patients with *VHL* syndrome have both benign and malignant neoplasms, including cysts and, in 7–12 % of cases, there are neuroendocrine tumors [12]. Most of these tumors are slow-growing. Diagnosis is carried out using MRI and endoscopic ultrasound. If the tumor is more than 2.8 cm and there are no metastases, surgical treatment is indicated. If the tumor is no more than 2.8 cm, dynamic control is required [13]. The tumor of the endolymphatic sac of the inner ear is found in 11 % of patients, which is benign, often bilateral and clinically manifested by deafness, tinnitus, dizziness and imbalance. Treatment is surgical [14, 15]. In 25–60 % of men during US, papillary cystadenoma of the epididymis is visualized, and in women a tumor of the broad ligament of the uterus (isolated cases are described). Masses, as a rule, are benign and do not require treatment [16]. About 20 % of patients with de novo mutation in the *VHL* gene do not have a family history, while in the prevailing percentage of cases (up to 80%) there is a hereditary history, which opens up the possibility of regular screening for the majority of patients [12]. According to the recommendations, the management of patients with confirmed *VHL* syndrome from an early age (2–5 years) should include an annual ophthalmological examination, analysis of methylated catecholamines, from the age of 11 years — MRI of the brain and spinal cord at least 2 times a year and an annual abdominal ultrasound, replaced by CT from 20 years. In the absence of manifestations of the syndrome, the frequency of examinations is reduced: Brain MRI every 3–5 years and abdominal CT every 2 years [2, 6, 17]. As patients grow older, genetic counseling at the stage of preconception care with an explanation of possible risks, as well as with consideration of possible pre-implantation genetic diagnosis is of great importance when planning their families [3, 18]. Surgical treatment of individual components of the syndrome, such as tumors of the pancreas and kidneys, require joint postoperative follow-up by an endocrinologist and a surgeon, for the purpose of timely optimal management of possible complications: disorders of carbohydrate metabolism and secondary hyperparathyroidism secondary to renal failure after resection of the kidney. The most dangerous consequence of bilateral adrenalectomy for pheochromocytoma is undoubtedly adrenal insufficiency, when complex therapy with the inclusion of not only glucocorticoids but also mineralocorticoids is required [19].

Conclusion

The presented clinical case confirms the fact that von Hippel-Lindau syndrome is a severe comorbidity requiring a multidisciplinary approach to examination, treatment and observation. Due to the high penetrance of the pathological gene, early genetic examination and detection of mutation carriers allows regular screening for the spectrum

of its constituent pathologies to ensure timely diagnosis and treatment.

Conflict of interests

The authors declare no conflict of interests.

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THE PHENOMENON OF NEUROPLASTICITY IN THE MECHANISMS OF REFLEXOTHERAPY

Abstract

Reflexotherapy (Chen-Chiu, acupuncture) is one of the most important and valuable part of mankind's heritage. Reflexotherapy has a long history and was formed as a practical healing method. Reflexotherapy methods include: acupuncture (Chen); Chiu-method (cauterization or warming of acupuncture points by means of wormwood or coal cigars); multi-needle stimuli by a special hammer; vacuum effect on acupuncture points; acupressure; tsubo-therapy; and hirudotherapy. Modern modifications of reflexotherapy are applied: electroacupuncture, electropuncture, laser reflexotherapy, craniopuncture, magnetopuncture, cryotherapy, color and light therapy, and others. There are many theories about the mechanism of action of this method. The focus of the Kazan school is on the role of sensory interaction at different levels of the nervous system in the implementation of the relexotherapy effects. The reflex mechanism for the development of therapeutic effect is considered in this connection as part of a universal method of information processing — sensorimotor interaction. The therapeutic effects of reflexotherapy are realized through the formation of local and background sensory flow, and their interaction at different levels of the nervous system. Afferent flow is processed at the peripheral, spinal-segmental, stem, subcortical levels, as well as at the level of the cortex. The realization of the positive effects of reflexotherapy occurs, including due to the phenomenon of neuroplasticity, which is implemented at the peripheral and central levels. Reflexotherapy methods can activate the phenomenon of brain neuroplasticity, leading to structural and functional changes that require further research in this direction.

Key words: *reflexotherapy, neuroplasticity*

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Reflexotherapy (Chen-Chiu, acupuncture) is an important and valuable legacy of both traditional oriental medicine and humanity as a whole. This is the only method of treatment that, having arisen thousands of years ago, has been preserved and is now used in a form very close to the original. Reflexotherapy has a long history and was formed as a practical therapeutic method. From ancient times it was noticed that injections in some points not only alleviated the course of several diseases, but sometimes even completely cured people. Therefore, it is recommended not to neglect ancient empiricism, it is often possible to derive something significant for modern science and practice [1]. The combined use of physical stimulation and mental stress has long been known in traditional medicine. Only now are scientists beginning to understand how to explain the effectiveness of these traditional practices in terms of Western medicine. Western medicine has ignored Eastern medicine for a long

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time, although millions of people have used the latter for thousands of years. [2]

Reflexotherapy is thought to have originated in Buddhist temples in Nepal or Tibet. The development of this method lasted for several centuries. Chen-Chiu (reflexotherapy) later became widespread not only in China but also in Korea, Japan, Burma, Mongolia, Vietnam, and India. In Europe, in particular in France, the method penetrated around the 13th century. Doctors described their observations of the good results of reflexotherapy in the treatment of multiple chronic diseases of internal organs, neuralgia, myositis, rheumatism, acupuncture anesthesia (analgesia). In Russia, Professor of Medical Surgery Academy P. Charukovsky, who noted a positive therapeutic effect for rheumatism and sciatica [3], applied the method of reflexotherapy in 1828. Interest in reflexotherapy in our country increased in the middle of the XX century. To date, the efficacy of this method is still studied by modern medicine, and it is obvious that the method of reflexotherapy has great success in the treatment of people with various diseases. Specialists in internal and general medicine mainly practice reflexotherapy.

The methods of reflexotherapy include: acupuncture (Chen); Chiu-method (burning or warming of acupuncture points using coal or wormwood cigars); multineedle exposure by a special hammer; vacuum exposure on the acupuncture points; acupressure; tsubo-therapy; and hirudotherapy. Modern modifications of reflexotherapy are also applied: electroacupuncture, electropuncture, laseromagnetotherapy, craniopuncture, magnetopuncture, cryotherapy, color and light therapy and others.

There are a lot of theories about the mechanisms of action of reflexotherapy. Eastern doctors, that had been using the method of Chen-Chiu since ancient times, sought to understand its essence, to explain the mechanisms of action. The theoretical concepts of the Ancient East thinkers have become fundamental for the interpretation of many natural phenomena and explanation of the reflexotherapy mechanism. Two fundamental philosophical concepts — the theory of Yin-Yang and the theory of the five elements (Wu-Hsing) — became the theoretical basis for all kinds of scientific activities of the peoples in the Ancient East, including medicine [4, 5]. For modern scientists, these concepts look archaic, but they are facts, concepts and hypotheses based on the spontaneous materialistic views of ancient doctors that have been proved over many centuries.

Most studies conducted by Western European scientists are mainly aimed at studying the mechanism of certain aspects of acupuncture effect on the human body. Therefore, there is a significant number of theories explaining the mechanisms of reflexotherapy. Most theories are based on defined, concrete facts: capillary theory, tissue theory, histamine theory, flocculation theory, electrical theory, thermoelectric theory, ion theory. Attention is paid to organ neurocutaneous relationships and reverse skin neuro-organic relations. Most authors suggest that the therapeutic effect of reflexotherapy is based on the effect on the central nervous system, through which the regulating and trophic effect on the impaired functions of the body is carried out [6].

Numerous studies of domestic reflexotherapy schools also offered a sufficient number of theories. The focus of the Kazan School is on the role of sensory interaction at different levels of the nervous system as the way for the implementation of reflexotherapy effects. The reflex mechanism of the development of the medical effect is considered in this connection as part of the universal method of information processing — sensorimotor interaction [7]. The principle of sensory interaction was articulated for the first time by R.A. Durinyan to explain the mechanisms of auricular reflexotherapy [8].

The practical basis of acupuncture is controlled sensory flow. Of the existing five sensory analyzers — extractive proprioceptive, visual, auditory, gustatory and olfactory — the extractive proprioceptive one is used in the practice of acupuncture. Exposure of the acupuncture point by various methods leads to the excitation of sensory afferent flow. Therapeutic effects of reflexotherapy are realized through the formation of local and background sensory flow, and their interaction at different levels of the nervous system. According to G. A. Ivanichev [7], the following main levels of sensory systems are distinguished:

- Peripheral level,
- Spinal segmental level,
- Stem level,
- Subcortical level,
- Cortical level.

The **peripheral level** of sensory systems is represented by receptors. In the receptors of the acupuncture point, irritation is registered and coded for transmission to other parts of the nervous system. In the receptors, the energy of the stimulus is transformed into a nerve impulse of the sensory fiber. Irritation of acupuncture points causes local reactions in the form of color changes of the skin, its blood supply, temperature, moisture, sensitivity. Anatomically and histologically, an acupuncture point is the most concentrated cluster of nerve elements located at different depths and different tissues. A limited number of receptors located at different depths in the skin, fascia, periosteum, muscles, vessels and nerves, available to irritation from the body surface, take part in the implementation of acupuncture therapeutic effects. In the receptors of the acupuncture point, irritation (the action potential of the sensory fiber), the coding of this irritation and its transfer to the segmental apparatus of the spinal cord are recorded.

The second reaction is a segmental response to stimulation of the exposure point. Thus, the nerve impulse (the potential of the sensory fiber) that has arisen in the receptors reaches the first relay station for processing the afferent (sensitive) flow in the central nervous system — the spinal cord with peripheral sensory nerves — **the spinal segmental level.** The bodies of neurons, which are the structural, functional and genetic unit of the nervous system, represent the gray matter of the spinal cord. Neuronal processes provide a nerve impulse from receptors or other neurons to the following neurons, as well as to the periphery to efferent performers. The spinal cord with peripheral sensory nerves is the first relay station for processing afferent flow. The reception, gate control, and further processing of the primary product to the next part of the nervous system are carried out here [7].

Segmental reaction is expressed by the direct reaction of the segment with the inclusion of the fibers of the autonomous nervous system to various formations (internal organs, vessels, muscles, etc.). To obtain a stable segmental reaction, a certain exposure time is necessary, since short-term stimulation can result in rapid attenuation of the reflex. In classical acupuncture, such cases pertain to inhibitory techniques. Apparently, in some cases, this response is the main one in reflexotherapy, especially if it is local segmental influence of points. It is also possible that the therapeutic effect of exposure on messenger points of Zakharyin-Ged zones, simply pain points is based on such communication. In the process of human evolution, the principle of segmental innervation has changed significantly (it is observed only in the early stages of embryonic development). The appearance of the brain has significantly complicated segmental relationships, although the basic principle of segmental innervation has been preserved. Moreover, in the process of evolution, nature „re-insured itself", each metamer began to innervate not at the expense of one segment, but it was overlapped by neighboring ones (upper and lower). Such phenomena are extremely important in clinical practice. Relationships at the level of the segmental apparatus are extremely complex; many issues in their detailed functioning are not fully understood. For example, the role of the so-called transition segments is poorly understood. It is known that vegetative centers are located in the lateral horns of the spinal cord and are located at the level of C_8 — L_2 (sympathetic) and S_2 — S_5 (parasympathetic). [9, 10] According to W. Schneidt, 1952; G. Bachmann, 1961, through these segments (C_8 and S_2) communication can be carried out between motor fibers of the vagus nerve at the top tractus parependimalis in lower parts. At the same time G. Bachmann notes that the main points of acupuncture (toning, inhibitory, points-sources, lo-points, etc.) are located in the areas of innervation of these segments or near them. This interpretation of the role of transitional segments deserves attention. If we consider that the vagus nerve evolutionarily had a significant somatic part, partially preserved, as well as a close connection with the trigeminal nerve (their common core — nucleus ambiguus), then, indeed, mutual influences and information transfer are possible, bypassing the classical pathways of the brain and spinal cord.

From segmental formations, nerve impulses along specific and nonspecific pathways of the spinal cord are directed to the subcortical stem structures (reticular formation, thalamus and hypothalamus, pituitary, limbic system and other formations) and, finally, to the cerebral cortex. There is also feedback between all these formations. The perception of irritation by different structures of the brain depends on the specificity of the structures themselves and

the area where the irritation is applied. Typically, the more functionally important is an organ or an area of the body, the more widely it is represented. This applies, for example, to the face, tongue, mouth, arms, especially the hands, and partly to the feet. Probably, it should be expected that the application of irritation to the areas of the body functionally more differentiated, with a higher density of nerve endings (limbs, face) will be perceived much more fully than, for example, in less differentiated areas (back).

In the practice of acupuncture, this assumption is fully confirmed. The known main acupuncture points (toning, inhibitory, lock, etc.) are located mainly in the distal extremities. The same applies to the points of „first aid", located in the mouth and at the fingertips. It is naturally, that the functionally differentiated massive representation of the marked body areas will have a stronger impact than the irritation of poorly differentiated areas. Hence, the distal points are the main points and have a general regulatory action (according to traditional concepts, the regulation of „energy" in general). They act stronger than, for example, the points on the back (in the classical version — the points of sympathy), which have a local segmental nature of the impact [11].

The stem level of sensory systems is structurally represented by the posterior, which includes the medulla and cerebellum, middle and intermediate brain. The emergence of the medulla oblongata is associated with the development of statics, acoustics and gill apparatus involved in the formation of the respiratory and circulatory systems. Many vital autonomic reflexes involving reticular formation, the nucleus of four pairs of lower cranial nerves (IX, X, XI, XII) and other structures are mediated through the medulla oblongata. The substance of the reticular formation contains vital respiratory and vasomotor centers, functionally closely related to the vagus nerve. The sensory input system of the medulla oblongata is represented by the afferent pathways of the vagus, pharyngeal and vestibular-cochlear nerves [7, 8, 10]. From the point of view of acupuncture, IX, X pairs are important, because we can influence their afferent channels. The receptive field of the vagus and pharyngeal nerves, available to acupuncture, is located on the ear in the area of the external auditory canal, bowl (cimbala conchae) and the cavity of conchea (cavum conchae). These areas include the points of the following areas: XIV — adjacent to crus of helix, XV — the bowl of conchea, XVI — the cavity of conchea [6, 8]. An important sensory area is a three-sided fossa (X area) — on reflex effects on a number of visceral reactions is not much inferior to conchea, due to its origin, formation and innervation (V, VII, IX, X pairs of cranial nerves). Reflex reactions, caused by this area of the auricle, should be by nature close to those, which are caused by the area of the conchea, and differ only in the topography of its implementation. If the conchea is the area of reflex reactions to the functions of the thoracic and abdominal cavities, the trilateral fossa is the area of reflex reactions to the functions of the pelvic organs, in particular to the terminal functions of the genital and excretory organs, the regulation of which is associated not only with the autonomic nervous system, but also with the somatic one. The presence of somatic afferent innervation of the trilateral fossa region with branches of the trigeminal nerve (in contrast to the conchea region, where this is practically absent) is necessary because the function of the pelvic organs is sufficiently strongly corticalized and well amenable to arbitrary (conscious) control. To influence these functions, it is necessary to involve thalamocortical projections in the activity, which is easily achieved when the trigeminal system is activated, thanks to its powerful thalamocortical projections [8].

The trigeminal nerve system, through which a functional multilateral connection with various afferent systems of the brain stem is carried out, has a great importance in the implementation of the effects of reflexotherapy. The sensory input system of the afterbrain includes a large diverse receptive field of the trigeminal nerve (head and neck part), bounded by extractives of the facial nerve (bowl of the ear). The main afferent system of the head is a powerfully organized anatomical and functional structure of the trigeminal nerve. The ascending afferent flow from the trunk is controlled by the trigeminal nerve, so the acupuncture points in the trigeminal nerve system have greater activity in comparison with the points located on the trunk [7, 8].

The midbrain is an entity that has brought together all the afferent pathways and is of great importance in controlling sensory flow. The reticular formation

plays a special role in the activation and inhibition of brain activity. The generalized background activity of the reticular formation is supported by a converged afferent flow formed by all types of analyzers. In this case, the reticular formation can selectively activate or inhibit the motor, sensory, visceral, behavioral systems of the brain. The reticular formation controls the transmission of sensory information through the nucleus of the thalamus. It should be emphasized that in the implementation of reflexotherapy effects, especially general reactions, the functions of the middle brain have an important place [7, 9, 10].

The structure of the intermediate brain, which ensures the integration of homeostatic reactions of the body and the design of behavioral and emotional reactions, is the hypothalamus. Powerful afferent connections of the hypothalamus with the olfactory brain, basal ganglia, thalamus, hippocampus, orbital, temporal and parietal cortex determine its awareness of the state of almost all brain structures. The hypothalamus itself provides information to the thalamus, reticular formation, vegetative centers of the trunk and spinal cord. Due to the large number of input and output connections, polyfunctionality of structures, the hypothalamus performs the integrating function of vegetative, endocrine and somatic activity [9, 10]. In the practice of acupuncture points of the cervical area and auricular points of tragus area, intertragic notch, posterior auricular grooves and antitragus are used to influence the functional state of the hypothalamus. The points of general action that increase the activity of non-specific brain systems determine the stability of numerous processes implemented by the hypothalamus [7].

The structure in which the processing and integration of almost all signals going into the cerebral cortex from the neurons of the spinal cord, mid and medulla oblongata, cerebellum, pale ball, from the visual, auditory, gustatory, skin, proprioceptive analyzers, from the nuclei of cranial nerves take place, is the thalamus. The ability to obtain information about the state of many body systems is provided by about 120 multifunctional nuclear groups of the thalamus. Nonspecific and associative nuclei make up the bulk of the neural substance of the thalamus. The main flow of information is processed by nuclear formations and the most significant part is delivered to the cerebral cortex. The activity of specific thalamus nuclei has a special place in the realization of many effects of reflexotherapy. The corporeal sensory flow is collected in the posterior ventrolateral nuclear complex and from the face through the trigeminal nerve system — to the posterior ventromedial nuclear complex. Thus, two afferent flows have relatively independent existence for subsequent transformations [5, 7, 12]. Thus, the thalamus is the highest center of sensory information control.

The subcortical level, the afferent organization of basal ganglia functions, mainly focuses on supporting functions of extrapyramidal motility organization. The limbic system is the oldest part of the cerebral cortex, located on the inner side of the cerebral hemispheres. It includes hippocampus, cingulate gyrus, amygdala, bulb-shaped gyrus. Limbic formations belong to the higher integrative centers of regulation for vegetative functions of the body. The neurons of the limbic system receive impulses from the cortex, subcortical nuclei, thalamus, hypothalamus, reticular formation and all internal organs. The limbic system is involved in afferent synthesis, in the control of electrical activity of the brain; it regulates metabolism and provides a number of vegetative reactions. A characteristic feature of the limbic system is the presence of well-defined ring neural connections that unite its various structures. Thus, the structures of the limbic system are involved in the implementation of such complex brain functions as behavior, emotions, learning, and memory. The limbic system is involved in the implementation of therapeutic effects of acupuncture in combination with thalamus, hypothalamus, reticular formation [5, 7]. Among the structures responsible for memory and learning, the hippocampus and the associated posterior zones of the frontal cortex play a major role. Their activity is important for the transition of short-term memory to long-term memory. The hippocampal complex is highly sensitive to hypoxia and at the same time is characterized by a unique plasticity, which explains the important role of this structure in the genesis of epileptic seizures, as well as in learning and memory. In addition, it is the main center of neurogenesis of the mature brain.

Neurogenesis in the adult brain is a phenomenon relatively recently recognized by the scientific

community, which has disproved the long-standing scientific theory about the static nature of the nervous system and its inability to regenerate cells. It is now generally accepted that neurogenesis is constantly occurring in two limited areas of the brain — the hippocampal subgranular area (HSA) and the subventricular area (SVA) of the lateral ventricles. New neurons formed in the HSA migrate to the layer of granular cells of the hippocampal dentate gyrus [13]. Neurons generated in SVA enter a new associative cortex, entorhinal cortex, and olfactory bulb [14, 15]. Recent studies have shown that newly formed neurons in the adult brain are embedded in existing neural networks and receive functional inputs [16]. Neurogenesis in the adult brain is regulated by physiological and pathological factors at all levels, and new neurons may be necessary for certain brain functions, such as learning and memory. Recent work demonstrates neurogenesis in a number of other brain structures: in the caudate nucleus, frontal cortex, primary and secondary motor and somatosensory cortex [17, 18]. It was recently shown that in primates, newly formed neurons from the subventricular area can migrate to the striatum, which is responsible for complex motor reactions and the formation of conditioned reflexes [19]. Thus, two afferent systems pass through the brain stem into the cerebral cortex: one — specific — all specific sensitive pathways, carrying impulses from all receptors (extra, inter-and proprioceptors) and ending on the bodies of cells mainly of the 4th layer of the cortex; another — nonspecific, formed by reticular formation and ending on dendrites of all layers of the cortex. The interaction of both these systems determines the final reaction of cortical neurons.

The cortical level of sensory systems includes somatosensory and associative areas of the cerebral cortex. At this level, there is a conscious processing of the sensory flow, including nociceptive. Sensory areas of the cortex are areas in which sensory stimuli are projected. They are located mainly in the parietal, temporal and occipital lobes. Afferent pathways to the sensory cortex come mainly from specific sensory nuclei of the thalamus (central, posterior lateral and medial). The sensory cortex has well defined 2 and 4 layers (granular). Areas of the sensory cortex, irritation or destruction of which cause clear and constant changes in the sensitivity of the body, are referred to as primary sensory areas (nuclear parts of the analyzers, as believed I.P. Pavlov.) They consist mainly of monomodal neurons and form sensations of the same quality. In primary sensory zones, there is usually a clear spatial (topographic) representation of body parts, their receptor fields. Around the primary sensory areas, there are less localized secondary sensory areas, polymodal neurons, which respond to several stimuli. The most important sensory area is the parietal cortex of the postcentral gyrus and the corresponding part of the postcentral lobule on the medial surface of the hemispheres (fields 1–3), which is designated as the somatosensory area. There is a projection of the skin sensitivity of the opposite body side from the tactile, pain, temperature receptors, interoceptive sensitivity and sensitivity of the musculoskeletal system, from muscle, joint, tendon receptors. The projection of the body areas in this area is characterized by the fact that the projection of the head and upper trunk is located in the lower lateral areas of the postcentral gyrus, the projection of the lower half of the trunk and legs is located in the upper medial areas of the gyrus, and the projection of the lower leg and feet — in the cortex of the postcentral lobule on the medial surface of the hemispheres. The projection of the most sensitive areas (tongue, larynx, fingers, etc.) has relatively large areas compared to other parts of the body. Most of the information about the outside world and the internal environment of the body, received in the sensory cortex, is transmitted for further processing in the associative cortex.

Associative areas of the cortex include areas of the new cerebral cortex, which are located near the sensory and motor areas, but do not perform directly sensitive or motor functions. The associative cortex is the phylogenetically youngest region of the new cortex, most developed in primates and humans. In humans, it makes up about 50 % of the entire cortex or 70 % of the neocortex. The main physiological feature of neurons in associative cortex that distinguish them from neurons in the primary areas is polysensority (polymodality). They respond with almost the same threshold not to one, but to several stimuli — visual, auditory, skin and others. The polysensority of neurons in the associative cortex is created both by its corticocortical connections with different projection areas, and its

main afferent input from the associative nuclei of the thalamus, in which there has already been complex processing of information from various sensitive pathways. As a result, the associative cortex is a powerful device for the convergence of various sensory excitations, allowing performing complex processing of information about the external and internal environment of the body and using it for the implementation of higher mental functions. Thus, sensory support of the central mechanisms in nervous regulation is crucial for the integration of numerous functional physiological systems of the body. Brain functions are organized so that the more complex is the function, the more branched neural networks are involved in its organization.

Perhaps the implementation of reflexotherapy effects on the cortical level is due to the phenomenon of neuroplasticity (modulation of neurogenesis). The use of acupuncture, Chiu-method, multineedle irritation, craniopuncture, as well as other methods of influence on the distal, local, facial, auricular points, as well as systems of wonderful meridians, causes a controlled afferent flow, with which it is possible to affect various areas of the cerebral cortex. Afferent flow is treated at the peripheral, spinal-segmental, stem, subcortical levels, and sensory interaction occurs at the level of the cortex. Due to the properties of neuroplasticity, the human body includes its own self-healing resource. We assume that reflexotherapy due to sensory interaction at different levels of the nervous system leads to the activation and inclusion of previously inactive neuronal connections to the process of functioning; perhaps, that positive effect of reflexotherapy leads to the formation of new synapses by the sprouting of fibers in preserved cells, new nerve cells (neurogenesis); migration of glial elements; re-organization of neuronal circuits with the formation of new sequence relationships, providing performance of lost functions (neoneurogenesis).

The processes of neuroplasticity are largely determined by the afferent component, which also affects the provision, modification and implementation of motor control and determines its flexibility/dynamics depending on the current need [20-23]. This leads to the fact that the cortical representation areas can vary depending on the incoming sensory information [22, 24]. The afferent system has significant potential for compensation, which is largely due to the considerable length and abundance of sensory fibers even at the cerebral level [25].

The basis of this biological phenomenon is the ability of various parts of the central nervous system to reorganize both due to structural changes in the brain substance, including qualitative and quantitative neuronal rearrangements, and due to the functional systems of the central nervous system, changes in neuronal connections and glial elements [21, 23, 26], as well as the development of new sensorimotor pathways and integrations in the central nervous system during recovery [27].

Neuroplasticity processes in the central nervous system occur at different levels (molecular, cellular, synaptic and anatomical) involving large groups of neurons in cortical and subcortical structures [23]. Studies have shown that the brain changes with each action we perform, transforming its circuits so that they suited better to the task at hand. If some brain structures fail, others take over. The brain is not a mechanism consisting of rigidly linked parts. The brain is able to change its own structure and functioning [2].

The most common definition is [28] the one according to which neuroplasticity is considered as the ability of the nervous system to adapt in response to endogenous and exogenous stimuli through optimal structural and functional rearrangement. This ensures the adaptation of the body and its effective activity in a changing external and internal environment [29, 30].

For many decades, medicine and neurobiological sciences were dominated by the idea of the immutability of morphological and functional structure of the adult formed brain and inability of nerve cells for self-recovery [31, 32]. The ability of nervous tissue for structural and functional changes in neuronal networks and elements throughout life was discovered several decades ago and further demonstrated in numerous experimental, neurophysiological and neuroimaging studies Many experiments conducted on animals have shown that the functional organization of neuronal structures of the cerebral cortex can be subject to modulation in the learning process, as well as in the damage to the peripheral or central nervous systems [32-36].

Knowledge of pathophysiological mechanisms at macro- and microscopic levels, underlying neu-

roplasticity, can improve therapeutic approaches to the restoration of lost functions and improve the quality of life of patients with various diseases. To achieve the maximum possible effect, a rehabilitation strategy should be followed, based on the results of the study of the role of neuroplasticity in the restoration of impaired functions. It is necessary to take into account the important role of social and hygienic lifestyle factors that influence the processes of neuroplasticity, and, accordingly, have an undoubted impact on the efficacy of rehabilitation measures [37]. Neuroplasticity is of great importance for physiological development and training, for development of adaptive abilities and restoration of lost neural connections in case of their damage [23, 35, 38–40].

Even in cases where there are no spontaneous movements in the limb, physical rehabilitation can have a beneficial effect on the restoration of the brain. Long-term proprioceptive stimulation by performing passive paretic limb movements, according to functional magnetic resonance imaging, leads to increased activity of the sensorimotor and additional motor cortex [41].

Rehabilitation, in its essence, is the repeated performance of certain tasks, the purpose of which is to stimulate neuroplasticity that ultimately leads to the consolidation of the stereotype of one movement and inhibition of another one. With the help of functional neuroimaging methods, it was shown that activation of sensorimotor areas of the cerebral cortex could be caused by observation of any motor act, its mental image or passive training [42]. At the same time, the early start of more complex rehabilitation, including such elements as kinesiotherapy, therapy with induced restriction (constraint-induced movement therapy), electromyostimulation, transcranial magnetic stimulation, various logopedic methods, is of interest [43]. Also of interest are the rapidly developing methods of physical rehabilitation associated with the use of mechanotherapy, virtual reality technology, optimization of therapeutic exercises using isometric physical exercises, use of therapeutic suits, methods of biological feedback, as well as more widespread use of orthotic devices [44].

For natural stimulation of neurogenesis in the elderly, natural positive stimuli should be considered as „training“ and „supporting“ neurogenesis factors: favorable environment, mental activity, physical activity, low-calorie balanced diet [45-47]. A small group of studies comprises papers on neuroplastic mechanisms of reflexotherapy. The papers present data on the effects of acupuncture [48-50], electroacupuncture [51], Chinese medicinal plants [52, 53], craniopuncture [54] on neuroplasticity.

In recent years, the use of craniopuncture in practical reflexotherapy has been of great interest. When conducting craniopuncture, exposure is not isolated at one point, but embraces the whole area. There are more than 20 areas of the scalp, the stimulation of which has a therapeutic effect. It is believed that affecting the scalp area cause irritation of the receptors, afferent impulses (mainly nociceptive and protopathic) involving the structures of the medulla oblongata, subcortical nuclei, cerebral cortex and subsequent influence on various systems of the body. It should be emphasized that the localization of the reflex areas to a certain extent, coincides with the projection of the anatomical brain structures. For example, the sensory and motor areas correspond to the sensory and motor cortical regions, which are localized in the precentral and postcentral gyrus. The scalp areas are innervated by the structures of the trigeminal nerve and upper cervical spinal segments C2-C3, therefore their irritation causes a targeted effect on the segmental and suprasegmental structures of the brain, with particular importance of selective activation of various parts in the limbic-reticular complex, which provide adaptive functions by integrating emotional-motivational, vegetative and somatic reactions [8, 55]. Many leading reflexologists believe that cranial therapy has a direct impact on the cortical brain structures.

Despite the active study of the neuroplasticity problem, at the present stage of research, the question remains about what mechanisms can be used to influence the formation of new neurons in the brain, as well as what stages of neurogenesis these effects extend to. A sufficient level of adequate afferentation from the periphery is a condition and basis for normal reactions of the whole brain in the implementation of long-term processes of nervous regulation, providing a functional reserve of reliability. Keeping it in mind, we can count on the possibility of exposure to these mechanisms by methods of reflexotherapy.

The study of neuroplastic reflexotherapy mechanisms has not yet received proper development in clinical randomized trials. At the same time, these methods need to be confirmed not only by catamnestic results, but also by high-tech control methods, such as positron emission tomography and functional magnetic resonance imaging. The use of neuroimaging and neurophysiological methods allows to observe the processes of reorganization and plastic changes in the central nervous system [56].

The high clinical efficacy of reflexotherapy in the treatment and rehabilitation of patients opens up wide boundaries for further research. For the effective use, development and creation of new methods of reflexotherapy comprehensive scientific development of its foundations is needed. And such thorough scientific research will open up new opportunities for reflexotherapy. We intend to conduct research and study of neuroplastic reflexotherapy mechanisms, as the prospects of neuroplasticity theory are extremely great for both healthy people and people suffering from serious diseases. Perhaps, with the help of reflexotherapy methods, it is possible to influence the neuroplasticity mechanisms, which requires further research in this direction

Conflict of interests

The authors declare no conflict of interests.

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FATTY ACID COMPOSITION OF SERUM LIPIDS IN PATIENTS WITH DECOMPENSATED TYPE 1 DIABETES MELLITUS DEPENDING ON THE DIABETIC KETOACIDOSIS SEVERITY

Abstract

Summary. In diabetic ketoacidosis, significant metabolic disorders develop in all organs and tissues, including the myocardium. The main energy substrate in the myocardium are fatty acids. **The objective** was to study the fractional composition of serum in patients with T1DM, complicated by diabetic ketoacidosis (DKA), depending on the severity of DKA. **Materials and methods.** Determination of the fatty acid spectrum of serum lipids was carried out in the following groups of patients: 68 patients with compensated type 1 diabetes mellitus (group 1); 54 patients with type 1 diabetes complicated by mild ketoacidosis (group 2); and 42 patients with diabetes mellitus complicated by moderate and severe ketoacidosis (group 3). Extraction of lipids from serum was performed according to the method developed by J. Folh et al. (1957), after which methylation of fatty acids was carried out according to the method proposed by K. M. Sinyak et al., with subsequent analysis using the Crystal-2000M gas chromatograph (Russia). **Results.** All patients with type 1 diabetes mellitus compared with the group of healthy individuals showed an increase in the total content of saturated fatty acids, a decrease in the total concentration of unsaturated fatty acids, as well as an increase in the ratio of saturated / unsaturated fatty acids. At the same time, a significant difference between the studied groups was revealed. The most pronounced changes were found in the group of patients with type 1 diabetes mellitus complicated by moderate to severe ketoacidosis. **Conclusions.** These changes develop as part of a general systemic metabolic disorder in a given cohort of patients.

Key words: *type 1 diabetes mellitus, diabetic ketoacidosis, fatty acids*

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DKA — diabetic ketoacidosis, FAs — fatty acids, DM — diabetes mellitus, T1DM — type 1 diabetes mellitus, SFAs — saturated fatty acids, USFAs — unsaturated fatty acids

In recent years, there has been an increasing downward trend in the mortality rate due to true diabetic causes, such as diabetic coma as a result of ketoacidosis or hypoglycemia [2, 3]. According to the Register of Diabetes Mellitus (DM), as of 2017 this figure fell to 1.5 % [2, 3]. However, among other causes of death in patients with type 1 diabetes mellitus (T1DM), cardiovascular morbidity remains dominant (39.8 %): myocardial infarction, cerebrovascular disorders, chronic heart failure and acute cardiovascular events, such as cardiac rhythm disorders, pulmonary embolism, thrombosis, sudden cardiac death, cardiogenic shock, and cerebral edema [2, 3].

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In diabetic ketoacidosis (DKA), significant metabolic disorders develop in all tissues and organs. And myocardium is no exception [4, 5, 6]. It is well known that the main energy substrate for the cardiac muscle is fatty acids [4, 5, 7]. According to literature, they account for 60–70 % of the myocardium energy demands [4, 5, 7]. Medical literature extensively covers the changes occurring in the fatty acid composition of serum lipids in conditions, such as ischemic heart disease, hypertension, inflammatory and dystrophic conditions of the myocardium, acute alcohol-induced cardiac damage, etc. [1], and the study of fractional composition of serum lipids in patients with T1DM complicated by diabetic ketoacidosis (DKA), depending on DKA severity. However, the issue of how the fatty acid composition changes in patients with T1DM complicated by DKA, depending on DKA severity, remains poorly studied. One of the proposed mechanisms of development of cardiovascular disorders in patients with T1DM complicated by DKA can be impaired metabolism and composition of fatty acids.

Study objective: to investigate the fractional composition of serum lipids in patients with T1DM complicated by diabetic ketoacidosis (DKA), depending on DKA severity.

Materials and Methods

The fatty acid composition of serum lipids was studied in the following groups of patients: Group 1 — 68 patients with compensated T1DM; Group 2 — 54 patients with T1DM complicated by mild DKA; Group 3 — 42 patients with moderate and severe DKA. Patients in Groups 2 and 3 were hospitalized at the decompensation stage. T1DM and severity of DKA were diagnosed on the basis of the relevant criteria of National Guidelines for the diagnosis and treatment of DM patients, which relied on the therapeutic standards established by the WHO [2]. The mean age of the patients was 29.2±8.9 years. Blood sampling for the analysis was performed on day 1 after admission. The compensation of carbohydrate metabolism in Group 1 patients was confirmed by daily glycemia and glycated hemoglobin level. The control group included 32 healthy individuals without impaired carbohydrate metabolism and risk factors for cardiovascular diseases, who were comparable in gender and age to patients in Groups 1, 2 and 3.

Venous blood was used as study material. Lipids were extracted from serum by the method developed by J. Fohl et al. (1957), and then fatty acids (FAs) were methylated according to the method proposed by K. M. Sinyak et al. (1976), followed by analysis using the Crystal-2000M gas chromatograph (Russia). Fatty Acid Methyl Ester (FAME) Standard produced by Sigma (USA) was used for calibration. Peaks were calculated and identified using the Analytica for Windows software and hardware package based on IBM Pentium IV 1800. Concentrations of the following higher FAs were determined: myristic (C14:0), palmitic (C16:0), stearic (C18:0), palmitoleic (C16:1), oleic (C18:1), linoleic (C18:2ω6), α-linolenic (C18:3ω3), γ-linolenic (C18:3ω6), dihomo-γ-linolenic (C20:3ω6), and arachidonic (C20:4ω6).

Statistica 6.0 software package was used for statistical data processing. The significance of differences among the study groups was assessed using the non-parametric Mann-Whitney test. Differences at $p<0.05$ were considered statistically significant. The data were presented as median, 25th and 75th percentiles (Me 25p; 75p).

Results and Discussion

When analyzing serum concentrations of fatty acids in T1DM patients depending on the severity of DKA, we identified regular changes in the fatty-acid profile, as presented in the table below.

What attracts attention is the significant increase in the total content of saturated fatty acids (SFAs), the decrease in the total concentration of unsaturated fatty acids (USFAs), as well as the increase in the SFA/USFA ratio in all T1DM patients as compared to healthy individuals. Statistically significant differences among the study groups were found. The total content of SFAs in the group of patients with T1DM complicated by mild DKA increased by 12.9 % as compared to those in T1DM patients without DKA ($p=0.003$). This figure in the group of patients with T1DM complicated by moderate and severe DKA increased by 198 % as compared to that in T1DM patients without DKA, and by 6 % as compared to the patients with T1DM complicated by mild DKA ($p<0.001$).

Table 1. *Fatty acid composition of serum lipids in patients with type 1 diabetes complicated by diabetic ketoacidosis (Me (25th; 75th))*

Parameter	Control (healthy) (n=31)	Type 1 diabetes mellitus		
		No DKA (n=68)	Mild DKA (n=54)	Moderate and severe DKA (n=42)
C14:0,%	0.92 (0.67;1.19)	1.15 (1.01;1.92) $p<0.001$	1.13 (1.09; 1.46) $p<0.001$	2.16 (2.13; 2.36) $p<0.001$ $p_1<0.001$ $p_2<0.001$
C16:0,%	24.37 (21.69; 27.29)	28.96 (25.97; 30.09) $p<0.001$	30.86 (26.37; 32.68) $p<0.001$ $p_1=0.008$	32.8 (29.94; 35.68) $p<0.001$ $p_1<0.001$ $p_2<0.001$
C18:0,%	7.17 (5.66; 8.37)	6.88 (6.12; 8.26)	8.68 (7.52; 9.24) $p<0.001$ $p_1<0.001$	9.29 (8.55; 9.55) $p<0.001$ $p_1<0.001$ $p_2=0.003$
C16:1,%	3.19 (2.89; 4.82)	3.23 (2.51; 4.64)	2.78 (2.58; 3.48) $p<0.001$ $p_1=0.017$	2.53 (2.31; 2.78) $p<0.001$ $p_1<0.001$ $p_2<0.001$
C18:1,%	23.66 (20.62; 25.2)	23.85 (21.95; 25.37)	21.71 (20.31; 24.54) $p_1<0.001$	19.77 (18.92; 21.4) $p<0.001$ $p_1<0.001$ $p_2<0.001$
C18:3ω3,%	1.72 (1.35; 2.91)	1.53 (1.1; 1.71) $p<0.001$	1.24 (0.74; 1.6) $p=0.004$ $p_1=0.024$	1.15 (0.8; 1.29) $p<0.001$ $p_1=0.007$
C18:2ω6,%	31.74 (26.95; 34.32)	26.33 (24.45; 30.59) $p<0.001$	26.22 (24.54; 28.59) $p<0.001$	24.21 (23.59; 25.38) $p<0.001$ $p_1<0.001$ $p_2<0.001$
C18:3ω6,%	0.43 (0.33; 0.71)	0.95 (0.50; 1.53) $p<0.001$	1.32 (0.76; 1.42) $p<0.001$	2.07 (1.82; 2.36) $p<0.001$ $p_1<0.001$ $p_2<0.001$
C20:3ω6,%	0.92 (0.78; 1.09)	1.19 (0.96; 1.65) $p<0.001$	1.63 (1.22; 1.76) $p<0.001$ $p_1=0.007$	1.99 (1.39;2.1) $p<0.001$ $p_1=0.003$ $p_2<0.001$
C20:4ω6,%	4.17 (3.77; 7.28)	3.42 (2.69; 5.41) $p<0.001$	3.58 (2.9; 5.15) $p=0.001$	2.88 (2.57; 3.22) $p<0.001$ $p_1<0.001$ $p_2<0.001$

Table 1. *(The end)*

Parameter	Control (healthy) (n=31)	Type 1 diabetes mellitus		
		No DKA (n=68)	Mild DKA (n=54)	Moderate and severe DKA (n=42)
Σ polyunsaturated fatty acids	39.77 (37.02; 45.55)	34.5 (32.0; 39.75) ρ<0.001	33.67 (31.24; 37.04) ρ<0.001	32.1 (30.84; 33.94) ρ<0.001 ρ_1<0.001 ρ_2=0.01
Σ monounsaturated fatty acids	27.51 (23.6; 29.03)	23.36 (25.78; 31.22) ρ<0.001	24.67 (23.03; 27.5) ρ<0.001	22.31 (21.5; 23.58) ρ<0.001 ρ_1<0.001 ρ_2<0.001
Σ unsaturated fatty acids	66.9 (65.9; 69.24)	63.47 (61.81; 65.08) ρ<0.001	59.93 566; 62.6) ρ<0.001 ρ_1<0.001	54.62 5368; 55.65) ρ<0.001 ρ_1<0.001 ρ_2<0.001
Σ saturated fatty acids	33.08 (30.76; 34.1)	36.64 (33.8; 37.7) ρ<0.001	41.4 (35.56; 43.66) ρ<0.001 ρ_1=0.003	43.9 (42.35; 47.34) ρ<0.001 ρ_1<0.001 ρ_2<0.001
Σ ω6 acids	38.45 (35.8; 43.59)	33.1 (30.47; 37.23) ρ<0.001	32.33 (30.74; 35.95) ρ<0.001	31.23 (29.96; 32.44) ρ<0.001 ρ_1<0.001 ρ_2<0.001
Σ ω3 acids	1.72 (1.35; 2.91)	1.53 (1.11; 1.71) ρ<0.001	1.24 (0.74; 1.6) ρ=0.004 ρ_1=0.024	1.11 (0.8; 1.29) ρ<0.001 ρ_1=0.007 ρ_2<0.001
Saturated fatty acids / unsaturated fatty acids, units	0.49 (0.44; 0.52)	0.57 (0.53; 0.61) ρ<0.001	0.7 058; 0.76) ρ<0.001 ρ_1=0.005	0.81 (0.75; 0.87) ρ<0.001 ρ_1<0.001 ρ_2<0.001
Poly-/ monounsaturated fatty acids, units	1.32 (1.04; 1.54)	1.32 104; 1.54) ρ=0.016	1.37 137; 1.51) ρ=0.001	1.42 137; 1.58) ρ<0.001 ρ_1=0.005 ρ_2=0.034
ω3/ω6, units	0.04 (0.03; 0.06)	0.05 003; 0.05)	0.03 003; 0.05) ρ=0.006 ρ_1=0.037	0.03 (0.03; 0.04) ρ=0.006 ρ_1=0.006
Saturated / polyunsaturated fatty acids, units	0.81 (0.72; 0.91)	1.06 (0.91; 1.16) ρ<0.001	1.13 103; 1.27) ρ<0.001 ρ_1=0.003	1.41 (1.26; 1.48) ρ<0.001 ρ_1<0.001

Note: n — number examined; ρ — level of significance of differences compared to control; ρ_1 — level of significance of differences compared with the group without ketoacidosis; ρ_2 — level of significance of differences compared with the group of mild ketoacidosis

In analyzing concentrations of individual saturated fatty acids, it can be seen that statistically significant changes as compared to T1DM patients without DKA were observed only in concentrations of palmitic (C16:0) and stearic acids (C18:0) in the group of patients with T1DM complicated by mild DKA. These figures increased by 6.6 % (p=0.008) and 26.1 % (p<0.001), respectively, as compared to similar parameters in Group 1. It should be noted that the concentrations of stearic acid showed no statistically significant difference between the group of T1DM patients without DKA and healthy individuals. The most pronounced changes in all the SFAs studied were identified in the group of patients with T1DM complicated by moderate and severe DKA. The content of myristic acid (C14:0) was 87.8 % higher than in the group of T1DM patients without DKA, and 91.1 % higher than that in patients with T1DM complicated by mild DKA (p<0.001). As for palmitic (C16:0) and stearic (C18:0) acids, their concentrations in Group 3 was much higher than these figures in Groups 1 and 2. Concentrations of palmitic acid (C16:0) were 13.2 % and 6.3 % higher than those in the groups of T1DM patients without DKA (p<0.001) and patients with T1DM complicated by mild DKA (p=0.008), respectively. Levels of stearic acid (C18:0) were 35 % and 7 % higher than in the above-mentioned study groups, respectively (p<0.001; p=0.003 for Groups 2 and 3). Myristic acid (C14:0) concentrations in all of the study groups were similar to those in the control group. No statistical difference was found for this parameter between T1DM patients without DKA and with mild DKA. In contrast, the concentration of myristic acid (C14:0) in the group of patients with moderate and severe DKA was 87.8 % and 91.1 % higher than that in Groups 1 and 2, respectively, and the difference with the control group was 163.4 % (p<0.001).

The total content of polyunsaturated fatty acids in T1DM patients without DKA was 94.8 % of the level reported in the control group. The figure was 6.6 % higher than in patients with T1DM complicated by mild DKA, and 13.9 % higher than in patients with T1DM complicated by moderate and severe DKA. Differently directed changes were noticeable when considering concentrations of individual USFAs of serum lipids.

It should be noted that no statistically significant difference was identified, based on concentrations of palmitoleic (C16:1) and oleic acids (C18:1), between the control group and T1DM patients without DKA. On the contrary, concentrations of linoleic (C18:2ω6), α-linolenic (C18:3ω3) and arachidonic (C20:4ω6) acids in Group 1 were lower by 17 %, 11 % and 17.9 %, respectively, as compared to healthy individuals (p<0.001), and levels of γ-linolenic (C18:3ω6) and dihomo-γ-linolenic (C20:3ω6) acids were higher by 120 % and 29.3 %, respectively.

Statistically significant changes, as compared to the control group and T1DM patients without DKA, were observed in concentrations of palmitoleic (C16:1), oleic (C18:1), linoleic (C18:2ω6), α-linolenic (C18:3ω3), and dihomo-γ-linolenic (C20:3ω6) acids in both groups of patients with T1DM complicated by DKA. The concentrations of palmitoleic acid (C16:1) decreased by 12.8 % and 14 %, respectively, in the group of patients with T1DM complicated by mild DKA, and by 20.6 % and 217 %, respectively, in patients with T1DM with moderate and severe DKA (p<0.001). The concentration of oleic acid (C18:1) in serum lipids in Groups 2 and 3 was lower than that in T1DM patients without DKA by 9 % and 17.1 %, respectively (p<0.001). The reduction in α-linolenic acid (C18:3ω3) was 19 % and 24.8 %, respectively, for patients with T1DM complicated by mild DKA (p=0.024) and moderate and severe DKA (p=0.007). The most pronounced changes were identified in the USFA pool with respect to concentrations of γ-linolenic (C18:3ω6) and dihomo-γ-linolenic (C20:3ω6) acids. On the contrary, their concentrations increased in the groups of patients with T1DM complicated by mild DKA and moderate to severe DKA. The concentration of γ-linolenic acid (C18:3ω6) was 398 % and 117.8 % higher than that in T1DM patients without DKA, and 206.9 % and 3813 % higher than that in healthy individuals (p<0.001). Examinations of dihomo-γ-linolenic acid (C20:3ω6) concentrations in these groups showed a difference of 36.9 % and 67.2 %, respectively, as compared to Group 1 patients, and 77.1 % and 116.3 %, respectively, as compared to healthy individuals.

As for concentrations of monounsaturated acids, T1DM patients without DKA were not significantly

different from Group 2, and these figures were lower by 15.1 % and 10.3 %, respectively, as compared to healthy individuals. The concentrations of polyunsaturated acids were also lower in patients from the above-mentioned study groups and averaged 86.7 % and 88.3 % of the similar figures in healthy individuals ($p<0.001$). Changes in monounsaturated and polyunsaturated acids were also determined in the group of patients with T1DM complicated by moderate and severe DKA. The decrease in monounsaturated acids was 9.6 %, 4.5 % and 18.9 %, respectively, as compared to patients with T1DM complicated by mild DKA, T1DM patients without DKA, and healthy individuals ($p<0.001$). The decrease in polyunsaturated acids in Group 3 was 4.6 %, 6.9 % and 192 %, respectively, as compared to the above-mentioned groups.

The ratio of polyunsaturated and monounsaturated fatty acids in blood lipids increased in all of the study groups as compared to the control group. The most pronounced changes were identified in patients with T1DM complicated by moderate and severe DKA. These figures in patients of Group 3 were 3.6 % and 7.5 % higher as compared to patients with T1DM and mild DKA and T1DM patients without DKA and healthy individuals. It should be noted that no statistically significant difference was identified for this parameter between the groups of patients with T1DM complicated by mild DKA and those without DKA.

At the same time, there was a statistically significant increase in the SFA/USFA ratio due to the increase mainly in myristic acid (C14:0) and, to a lesser degree, in stearic acid (C18:0), and decrease in γ-linolenic (C18:3ω6) and dihomo-γ-linolenic acids (C20:3ω6).

The ratio of ω-3 to ω-6 polyunsaturated fatty acids in blood lipids showed statistically significant decrease in patients with T1DM complicated by DKA, irrespective of the severity of DKA, as compared to T1DM patients without DKA and the healthy individuals. No differences were found in the group of T1DM patients with DKA depending on DKA severity. The ω3/ω6 ratio was reported mainly due to reduction in concentrations of ω-3 fatty acids and relative increase in proportions of γ-linolenic (C18:3ω6) and dihomo-γ-linolenic (C20:3ω6) fatty acids.

Thus, our study identified significant changes in the fractional blood fatty acid composition in patients with T1DM complicated by DKA. The identified disorders were based on the imbalance of FAs expressed as a decrease in the pool of unsaturated fatty acids and an increase in that of saturated fatty acids. These changes develop as a part of general systemic metabolic disorders in the study cohort of patients.

Conflict of interests

The authors declare no conflict of interests.

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MODERN LIFESTYLE AND ITS IMPACT ON THE ULCERATIVE COLITIS INCIDENCE

Abstract

The objective of the study: To assess the significance of surrogate markers of the «hygiene hypothesis», the «old friends' theory» and the hypothesis of «depletion of biomes» in the development of ulcerative colitis among the population of Western Siberia. **Materials and methods:** An active survey (interviewing) of 81 patients with ulcerative colitis and 39 healthy respondents was conducted. The main surrogate markers of the «hygiene theory», the hypotheses of «old friends» and «depletion of biomes» were studied: past infestations, pets in childhood, use of antibiotics, breastfeeding, family size (number of siblings), attendance at pre-school institutions, accommodation in a dormitory while studying, accommodation in a city or a village, type of drinking water supply and the type of water respondents use for drinking; in the framework of the «biome depletion» theory, in addition to the markers listed above, a sugar consumption rate was assessed. Consumption of simple carbohydrates was calculated based on the number of cups of tea and/or coffee drunk per week and the number of teaspoons or cubes of sugar that the respondent puts in one cup. **Results.** Among the indirect markers of the «hygiene hypothesis» and the theory of «old friends» examined, only one effect the risk of ulcerative colitis among the population of the Omsk region — visiting preschool institutions (2I = 4.59, p <0.05). Of the indirect signs of the «biome depletion» hypothesis examined, significant differences were found in the amount of simple carbohydrates consumed: patients with ulcerative colitis had consumed more sugar with tea and/or coffee in the period before the first signs of the disease than healthy respondents (U = 1214.0; Z = 2.0; p = 0.04). **Conclusion.** In our study, the statistical significance of such factors as rare visits to kindergartens and the consumption of large amount of sugar by patients with ulcerative colitis in the period before the onset of the disease in comparison with healthy respondents was demonstrated.

Key words: *ulcerative colitis, «hygiene hypothesis», the hypothesis of «depletion of biomes»*

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IBD — inflammatory bowel disease, UC — ulcerative colitis

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Introduction

The main theory of the pathogenesis of inflammatory bowel diseases (IBD) is currently considered a disorder of immune regulation and activation of immune response against antigens of the intestinal microflora in genetically predisposed individuals under the influence of certain environmental factors. According to some scientists [1], the epidemiological trend towards the increase in IBD prevalence is associated with the improvement of the general hygienic conditions of modern society. One of the theories explaining the increase in autoimmune disease and various allergic reactions is the «hygiene hypothesis», which was articulated by David Strachan, an English epidemiologist [2]. This theory considers the influence of family size at an early age, attendance at preschool institutions and the presence of pets in childhood, living in a childhood with siblings that involves more contact with different microorganisms [3]. In contrast, the use of centralized water supply, filters for everyday needs, antibacterial wipes, soap, dishwashing detergents leads to a decrease in the antigenic effect on the body in childhood, which can be the cause of an excessive immune response in contact with microbes in adulthood. The rapid elimination of bacteria with antibiotics and modern hygiene products with antibacterial action makes it impossible to form an individual's own immunity against infections.

In 2003, Graham Rook proposed the hypothesis of «old friends» [4], the essence of which is that not only bacterial infections, but also infestations that occurred in childhood, play an important role in the formation of immunity. The difference of this theory from the «hygiene hypothesis» is that not all antigens of the environment are important for the harmonious development of immune mechanisms, but rather microorganisms and parasites («old friends») with low pathogenicity. Russian and foreign researchers consider [5] the «hygiene theory» and «old friends' theory» as contradictory, and their confirmation requires adequately designed studies. According to researchers, the first years of life have a special impact on the risk of autoimmune diseases. If during this period a child spends some time in kindergarten and in general frequently encounters infections, the risk of development of autoimmune diseases at an older age decreases [6, 7]. The study by Lopez-Serrano with co-authors [8] indicates an increased risk of IBD for people with higher education and high social level that also emphasizes the potential role of the «hygiene hypothesis» in their occurrence.

Part of the «old friends hypothesis» is the proposition that infestations have a significant impact on the formation of the immune system, and the last decades are characterized by a decrease in incidents of helminthiasis in economically developed countries. Immunomodulatory properties of helminths' metabolism products are studied in the treatment of autoimmune diseases, including IBD, multiple sclerosis, rheumatoid arthritis and type 1 diabetes [9]. In 2005 [10, 11] the effective influence of helminths on the treatment of IBD resistant to traditional pharmacological therapy was demonstrated. But subsequent follow-up has not confirmed the positive impact of helminthotherapy. Other studies prove that the interaction of helminths with the human body is not a symbiosis, as is the case with gut microbiota. Helminthiases require treatment [12], as they have adverse clinical consequences.

Finally, the hypothesis of «biome depletion» explains the increase in the incidence of IBD in terms of loss of species diversity and changes in the composition of the commensal microbiome in the human body [13]. Changes in microbiota diversity occur as a result of breastfeeding refusal in infancy, the use of antibacterial drugs, genetic predisposition. But the greatest impact on intestinal microbial community is due to dietary preferences («westernization») and changes in basic approaches to nutrition (widespread use of semi-finished products, sweeteners, preservatives, taste modifiers, etc.), various technologies for cooking and preserving food, modern methods of water purification. All these factors make a significant contribution to the increase in the prevalence of autoimmune pathology, according to a number of researchers [14-16].

Study Objective

To assess the significance of surrogate markers of the «hygiene hypothesis», the «old friends theory» and the hypothesis of «biome depletion» in the development of UC among the population of the Western Siberia region.

Materials and Methods

Retrospective case-control study was conducted during the period from 2016 to 2018. The initial data was collected in the form of an active questionnaire (interview). The study included all patients with UC hospitalized in the Department of Gastroenterology of the Regional clinical hospital of Omsk region for the specified period. The diagnosis of UC was established on the basis of clinical manifestations, characteristic endoscopic and histological changes of the colon, according to the clinical recommendations of the Russian Gastroenterological Association and the Association of Coloproctologists of Russia for the diagnosis and treatment of UC. The comparison was made with a control group consisting of healthy environment of researchers comparable in age (U = 13.38; p = 0.1760) and sex (2I = 2.72; p>0.05) with a group of patients with UC. All respondents gave voluntary informed consent and were included in the study.

The main group consisted of 81 patients (men — 42, women — 39) diagnosed with UC at the age of 18–79 years. The median age of patients at the time of the survey was 48 (32–60) years. The median age at the time of UC debut in all patients was 40 (28–54) years, in men — 40.5 years, in women — 32 years. The median time from the first symptoms of UC to diagnosis was 6 (1–12) months.

The control group consisted of 39 healthy respondents (men — 14, women — 25) aged 22 to 81 years. The median age of respondents was 46.0 (26.0–52.0) years. For men it was 36.0 ± 7.7 %, and for women — 64.0 ± 7.7 %.

We explored the major surrogate markers of the «hygiene theory», the «old friends hypothesis» and the «biome depletion» hypothesis: past infestations, pets in childhood, use of antibiotics, breastfeeding, family size (number of siblings), attendance at preschool institutions, accommodation in a dormitory while studying, accommodation in a city or village, type of drinking water supply and the type of water respondents use for drinking. Under the theory of «biome depletion», in addition to the above markers, a study of sugar consumption rate was carried out. Simple carbohydrate intake was calculated based on the number of cups of tea and/or coffee per week and the number of teaspoons or cubes of sugar that the interviewee puts in one cup. It was decided not to include in the study questions on education and social status, because they, in our opinion, are not indicators of a better hygienic condition.

Methods of descriptive statistics were used to systematize and describe the data. The median and interquartile range were used to describe the groups by quantitative characteristics. The frequency of qualitative features is given as a percentage, taking into account the standard error of the indicator. The Mann-Whitney U-test was applied to compare groups by quantitative characteristics. To compare the groups by qualitative characteristics, we used the calculation of 2I-statistics (Kullbak information statistics), considered as a variant of nonparametric analysis of variance. The results were considered significant at p <0.05. Statistical software package Statistica 6.1 was used for statistical data analysis.

Results and Discussion

According to the results of the study there were no statistically significant differences between patients with UC and healthy respondents in the presence of infestations in history, pets in childhood, taking antibacterial drugs, breastfeeding in childhood, place of residence, type of drinking water supply, allergies to food. Table 1 presents the results of the interview.

Families of parents in two groups of respondents were small (M–2.0 children). The main group had 48.1 ± 5.6 % of large families (3–7 children), and the control group — 43.6 ± 7.9 % of large families. There are no statistically significant differences between the groups (2I = 1.77; p > 0.05).

The analysis and comparison of frequency of visits to preschool institutions and accommodation in a dormitory for all respondents were carried out. It was found that kindergartens more often visited by healthy respondents 61.5 ± 7,8 % in comparison with patients with UC — 40.7 ± 5.5 % (2I = 4.59, p <0.05), and that fact was statistically significant. But there are no statistically significant differences between groups that lived in a dormitory at school (44.4 ± 5.5 % of patients with UC and 33.3 ± 7.5 % of the control group). The distribution of participants in the study on attendance of preschool institutions and accommodation in a dormitory at school is shown in Figure 1.

Table 1. *The results of the survey of ulcerative colitis patients on the main indirect markers of the «hygiene hypothesis»*

Questions, answer codes	Code 1 frequency in the main group, %	m	Code 1 frequency in the control group, %	m	2I-statistics	ρ
History of infestations (1 — yes, 2 — no, 3 — I do not know)	25.9	4.9	21.1	6.6	0.98	>0.05
Pets in childhood (1 — yes, 2 — no)	92.6	2.9	92.3	4.3	0.00	>0.05
Antibacterial drugs (1 — yes, 2 — no, 3 — I do not know)	25.9	4.9	30.8	7.4	0.96	>0.05
Breastfeeding in childhood (1 — yes, 2 — no, 3 — I do not know)	82.7	4.2	89.7	4.9	3.06	>0.05
Place of residence (1 — city, 2 — village)	39.5	5.4	43.6	7.9	0.18	>0.05
Type of drinking water supply (1 — centralized, 2 — non-centralized, 3 — centralized and non-centralized, 4 — imported water)	77.8	4.6	92.3	4.3	5.9	>0.05
Food allergies (1 — yes, 2 — no, 3 — I do not know)	13.6	3.8	15.8	5.9	1.44	>0.05

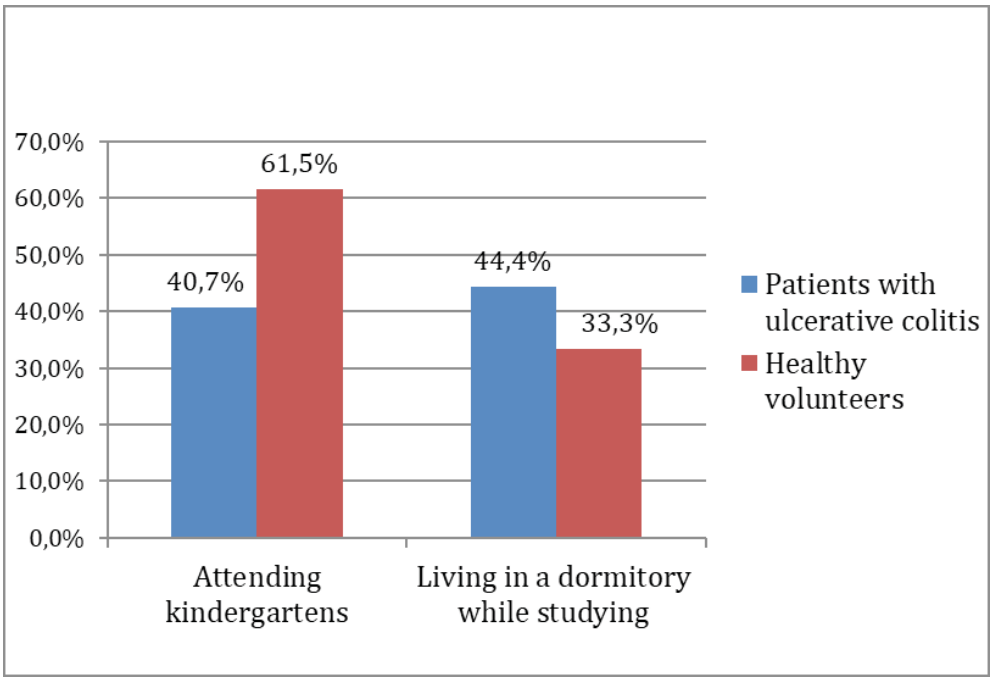

Figure 1. *Attending kindergartens and living in a dormitory while studying*

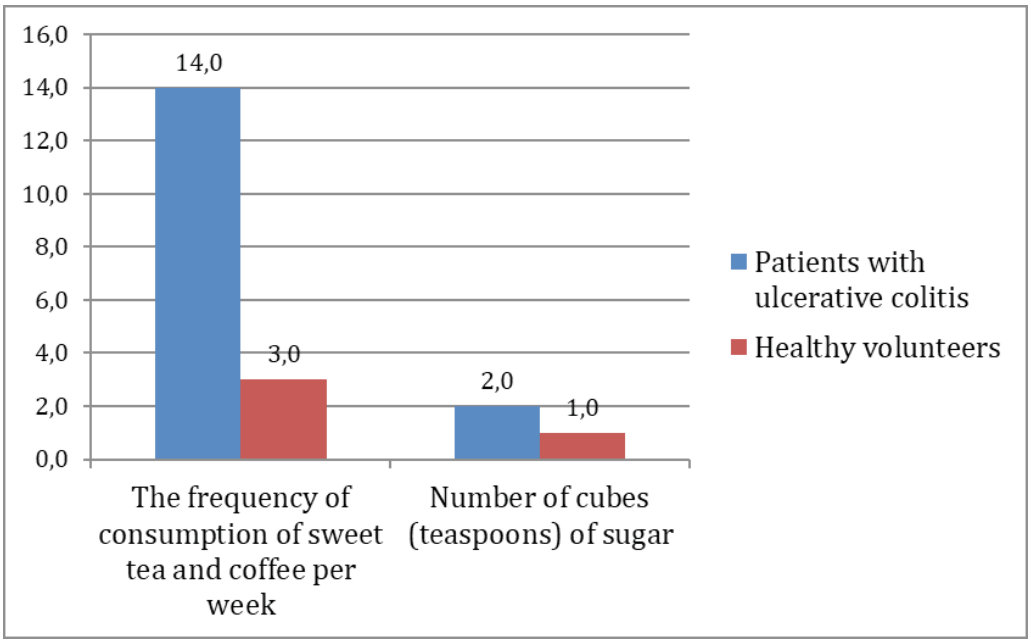

Figure 2. *Sweet tea and coffee use*

The «hygiene hypothesis» and the theory of «old friends» suggest that attending kindergartens has a beneficial effect on the harmonious development of the human immune system. Children's bacterial infections and infestations, which have low pathogenicity, play an important role in the formation of immunity.

There are no statistically significant differences between groups by type of drinking water supply and type of drinking water used. We analyzed such parameters of the type of drinking water supply as centralized, non-centralized, or both centralized and non-centralized, or imported water. When answering the question «What kind of water do you use to drink?» respondents chose between the following options: boiled, not boiled, settled, bottled, filtered. The survey showed that 33.3 ± 5.2 % of respondents in the main group and 33.3 ± 7.5 % in the control group used boiled water for drinking. At the same time, 77.8 ± 4.6 % of patients with UC and 92.3 ± 4.3 % of healthy respondents use centralized water supply.

Features of consumption of sweet tea and coffee in the study groups are shown in Figure 2.

Patients with UC have a clear tendency to more frequent consumption of these drinks with sugar (median — 14.0 (1.0–21.0) times a week) compared with healthy respondents (median — 3.0 (0.8– 14.0) times a week). However, there were no statistically significant differences between the groups in the frequency of consumption of tea and coffee with sugar during the week (p = 0.06). In addition, we found that patients with UC put statistically significant (p = 0.04) more cubes (teaspoons) of sugar in one cup of tea and/or coffee (2.0 (1.0–3.0) teaspoons; 1.0 (1.0–2.0) teaspoons, respectively). According to the «biome depletion» theory, the gut microbiota undergoes certain specific changes that occur not least under the influence of excessive consumption of food rich in simple carbohydrates.

Conclusions

Of the studied indirect markers of the «hygiene hypothesis» and the theory of «old friends», only one — attendance at preschool institutions (2I = 4.59) — affects the risk of UC in the population of Omsk region, p <0.05.

In the hypothesis of «biome depletion» significant differences were found in the consumption of simple carbohydrates: patients with UC consumed, in the period before the onset of the disease, more sugar with tea and/or coffee compared with healthy respondents (U = 1214.0; Z=2.0; p=0.04).

Our study demonstrated the contribution of such factors to the emergence of UC as rare attendance of preschool institutions and the consumption of a large amount of monosaccharides in patients with UC in the period before the onset of the first symptoms of the disease compared with healthy respondents.

Conflict of interests

The authors declare no conflict of interests.

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FEVER OF UNKNOWN ORIGIN: DESCRIPTIVE STUDY

Abstract

Background: fever of unknown origin is one of the diagnoses more difficult in our area, because it involves monitoring of a complex algorithm of several procedures to establish its cause and con frequently takes too long before any explanation. Therefore, the objective is to get to your diagnosis etiologic and to do a particular series of steps. **Objective:** to describe the most frequent causes of classical fever of unknown origin in the hospital setting and make a simplified diagnostic search algorithm for this pathology. **Methods:** a case-series study of 85 patients admitted to the Hospital Obispo Polanco with a diagnosis of fever of unknown origin conducted from 2013 to 2018 in the therapeutic services except for pediatrics and surgery units. The study variables included age, sex, complementary studies (variables from humoral, microbiological and biopsies), results obtained, diagnosis of each patient, treatment. **Results:** of all patients, 23 (27 %) had infections, of which 14 (16 %) of respiratory focus, 6 (7 %) of urinary focus, 2 (2 %) of abdominal focus and 1 (1 %) of the skin focus. Seven patients (8 %) had neoplasms, three of which (3 %) of respiratory origin, three of digestive tract (3 %) and one of prostatic origin (1 %). In four patients (5 %) were diagnosed of the rheumatic diseases. In 51 (60 %) patients not be could diagnose any cause of fever of unknown origin. **Conclusions:** the first cause of fever of unknown origin is diseases of unknown etiology with 60 % (51 cases) without being able to identify the clear focus. Among the known etiologies, the most private pathology is infectious bacterial diseases of the respiratory and urinary tracts (27 % — 23 patients). The third place is occupied by oncological diseases with a predominance of malignant pulmonary neoplasms (8 % — 7 patients). Rheumatological diseases occupy the last place and, in this study, accounted for only 5 % (4 patients).

Key words: *fever of unknown origin, infectious diseases, malignant tumors, algorithm of diagnostic search, treatment*

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ESR — erythrocyte sedimentation rate, HIV — human immunodeficiency virus, FUO — fever of unknown origin

Introduction

Fever of unknown origin (FUO) is a very difficult clinical «task» in the practice of many medical professionals, so it is very important to take into account a number of standardized steps that will allow you to make an etiological diagnosis of this pathology. For this reason, it is necessary to create a well-structured algorithm in order to make maximum use of the patient's hospitalization time and to identify the etiological factor as soon as possible.

In accordance with the criteria of R. B. Petersdorf and P. B. Beeson (1961), FUO was described as: repeatedly raising the temperature to 38.3 ° C for more than 3 weeks without establishing any

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diagnosis after one week of hospitalization. Subsequently, new criteria appeared by Durack and Street (1991), and currently FUO is defined as: a temperature of more than 38.3 ° C, recorded several times for more than 3 weeks, without establishing a diagnosis after 3 days of hospitalization or after 3 outpatient visits [1, 2].

This clinical syndrome is divided into four types: classical, FUO in patients with neutropenia, nosocomial type and FUO associated with infection caused by human immunodeficiency virus (HIV). There exists a huge variety of etiological causes that can cause FUO, among them there are four main groups: malignancies (Hodgkin's disease, colon cancer, pancreatic cancer), infectious processes (tuberculosis, endocarditis, cytomegalovirus, human immunodeficiency virus, intraabdominal abscesses, osteomyelitis), autoimmune and rheumatic diseases (temporal arteritis, rheumatic polymyalgia, systemic lupus erythematosus, systemic vasculitis) and other diseases (pulmonary embolism, drug fever) [1, 2, 3].

The purpose of our study was to describe the most common causes of FUO in inpatient conditions (the classic type of FUO), taking as a representative sample the cases diagnosed in the Obispo Polanco hospital over the previous 5 years (2013-2018); and, as a consequence, establish a single clinical diagnostic algorithm for the optimal use of additional examination methods.

Materials and methods

A descriptive study of a series of cases with 85 inpatients with a diagnosis of FUO at the hospital «Obispo Polanco» located in therapeutic departments, with the exception of the pediatric department and general surgery, was conducted during 5 years, in the period: March 2013 to August 2018.

Inclusion criteria: the study included patients aged over 18 years, male and female, with fever over 38.3 ° C and higher, lasting more than three weeks and hospitalized for more than one week without establishing the cause of the febrile syndrome.

Exclusion criteria: immunosuppressive patients were excluded from the study (with neutropenia — leukocytes less than 1000 / ml or neutrophils less than 500 / μl; HIV infection; hypogammaglobulinemia with IgG less than 50% of the norm (<7 g / l); being treated with prednisone or its equivalent for more than 2 weeks) and patients with a pre-established diagnosis of malignant neoplasm.

Clinical histories and discharge records of each patient were reviewed using the following collected data: age, gender, axillary temperature, symptoms accompanying febrile syndrome, additional laboratory and instrumental diagnostic methods performed, established diagnosis and treatment applied in each case.

All data was collected in an Excel document to create a single database with the percentage of each pathology that could cause a classic type of fever of unknown origin.

Results and discussion

According to the obtained results, the first step of specialists after conducting a thorough physical examination was the appointment of additional methods of laboratory diagnosis. Complete blood count with the determination of erythrocyte sedimentation rate (ESR), biochemical blood analysis, including C-reactive protein and procalcitonin, coagulogram and urinalysis.

Also, at the first stage of the survey, a microbiological analysis of blood, urine and feces, a Clostridium difficile toxin determination in the case of diarrhea syndrome, a human immunodeficiency virus serological test, antibodies to hepatitis B and C, serological tests for the detection of atypical pneumonia, brucellosis, toxoplasmosis, Epstein-Barr virus, mycoplasma, Q fever, chlamydia, Varicella Zoster virus, pneumococcal infection antigens and Legionella in the urine; in exceptional cases, in accordance with clinical suspicions, a microbiological analysis of nasopharyngeal aspirate and the thick drop method were prescribed.

The second stage, after the previous tests, was the expansion of the clinical examination by performing: the Mantoux test, chest X-ray, echocardiogram and abdominal ultrasound.

In the absence of a clinically significant result, additional invasive research methods were conducted, such as: gastroscopy, colonoscopy, bronchoscopy with biopsy, as well as computerized axial tomography of systems and organs, with possible involvement in the pathological process of FUO. After establishing the etiological diagnosis and discharge from the hospital, each patient underwent outpatient examination to further control the absence of fever and side effects of the prescribed treatment during the transition from intravenous antibacterial drugs when hospitalized for oral administration at discharge, and in the case of positive control, patients are observed annually in case of reappearance of symptoms. In the case of patients with an unspecified cause of FUO, at subsequent outpatient consultations, were observed additional new symptoms, full numbers were normalized in case of discharge with subfebrile body temperature, repeated physical examination, the effectiveness of empirical treatment and, if necessary, its correction in order to detect diagnostic prompts in the search possible etiology.

A total of 85 patients were studied, over the age of 18 years. The average age of all patients included in the study was 73 years, with a predominance of male — 59 patients (69%) and 26 patients (31%) of female sex.

The first etiological cause of FUO was infectious diseases in the case of 23 patients (27%), most of them of bacterial origin. In this group, fourteen patients with respiratory tract infections (16%) were identified, among whom five were confirmed using additional studies at the time of hospitalization and nine patients with clinical symptoms of respiratory tract infection, but with negative laboratory and instrumental methods at the time of hospitalization and confirmed later on outpatient consultation. In the latter case, these patients were given the diagnosis «Possible infectious focus of the respiratory tract» with suspicion of this type of infection due to the presence of clinical symptoms, but the inability to confirm it due to the negative result of additional studies.

In the case of six patients, urinary tract infections were detected (7%): in four patients this infectious focus was confirmed at the time of hospitalization in the inpatient unit, whereas in the case of the other two patients, symptoms of this type of infection were recorded, but with a negative result of additional laboratory tests, however, later the diagnosis was confirmed at the outpatient consultation, so they were assigned the diagnosis «Possible infectious focus of urinary tract» at the time of discharge. This group of patients is not included in the group «Unknown reasons of FUO», as this study is aimed at identifying the causes of febrile syndrome in a hospital, at the time of hospitalization of the patient, without taking into account the diagnoses established in the outpatient setting.

In the case of two patients (2%), infectious focus of the abdominal cavity were diagnosed with infectious gastroenteritis, confirmed on the basis of a clinical picture of diarrheal syndrome with pathological impurities and positive bacteriological examination of feces. Only in one case (1 %) was an infectious lesion of the skin in a patient with diabetes mellitus. Pulmonary tuberculosis was diagnosed in one patient (1%) using a Mantoux test and polymerase chain reaction for Mycobacterium tuberculosis with a positive result. The most frequent symptoms presented in this group were general deterioration, chills, shortness of breath, and dry cough.

The second reason underlying of FUO was malignant neoplasms in 7 patients (8%). In all cases, cancer tumors were diagnosed at a late stage. The following most common symptoms have been reported: asthenia, weight loss, shortness of breath, diarrheal syndrome with pathological impurities, such as blood and mucus.

Third place in the group of etiological factors took rheumatological diseases such as temporal arteritis,

systemic lupus erythematosus and rheumatic polymyalgia. The symptoms that represented the majority of patients in this etiological group were arthromyalgia, general stiffness, skin rash, pain at the level of the shoulder and pelvic girdle.

In 51 patients (61%) it was impossible to determine the etiological pathology of FUO even after a thorough physical examination to determine the morphological elements of the skin rash, damage to the oral mucosa, enlarged lymph nodes, enlarged thyroid gland, hepatomegaly and splenomegaly, cardiac murmurs, and rectal pathology manual study. In the absence of pathological signs, a complete algorithm of additional laboratory and instrumental examination methods (presented in Appendix 1 of this document), such as a complete blood count, ESR, urinalysis, biochemical blood count, C-reactive protein, proteinogram, ANA antibodies, anti-DNA, ANCA, rheumatoid factor, microbiological analysis of blood and urine, serological examinations for the presence of brucellosis, measles, toxoplasmosis, syphilis, cytomegalovirus, Epstein-virus, herpes simplex virus and Varicella Zoster, hepatitis B, C and A, HIV infection, Q fever, Legionella and Neumococo antigens in the urine, Mantoux test, electrocardiogram, chest X-ray, abdominal cavity (in 100 % of cases), negative results of which were repeated physical examination, ultrasound examination of the abdominal cavity, computed tomography (in the case of 41 patients), gastroscopy and colonoscopy, biopsy of the temporal artery (in the case of 32 patients in this group) — Table 1, Table 2, Diagram 1.

Patients in this group of descriptive studies observed a duration of febrile syndrome of more than 3 weeks before hospitalization (maximum duration of 2 months) and more than three days during their stay in hospital (as an important FUO criterion for inclusion in this study). In the case of 41 patients of this etiological group, the maximum duration of the febrile syndrome was 4 weeks, whereas in 10 patients the normalization of body temperature figures fell at the end of the first week — the beginning of the second week of hospitalization.

Table 1. *Distribution of etiological causes of FUO in relation to the total number of cases*

Etiological causes	Number of cases	Percentage (%)
Infectious diseases	23	27
Malignant neoplasms	7	8
Rheumatological diseases	4	5
Unknown reasons	51	60
Total number of cases	**85**	**100**

Note: FUO — fever of unknown origin

Table 2. *The distribution of etiological factors of FUO by diagnostic groups*

Diagnostic group	Number of cases
Infectious diseases	**23**
– Community-acquired pneumonia	**2**
– Bronchitis	**2**
– Pharyngitis	**1**
– Tuberculosis	**1**
– Confirmed urinary tract infection	**2**
– Intra-abdominal infection	**2**
– Possible infectious focus of the respiratory tract	**9**
– Possible infectious focus of urinary tract	**4**
Malignant neoplasms	**7**
– Pulmonary adenocarcinoma	**3**
– Adenocarcinoma of the colon	**2**
– Pancreatic adenocarcinoma	**1**
– Adenocarcinoma of the prostate gland	**1**
Rheumatological diseases	**4**
– Temporal arteritis	**2**
– Systemic lupus erythematosus	**1**
– Rheumatic polymyalgia	**1**
Without diagnosis	**51**
Total number of cases	**85**

Note: FUO — fever of unknown origin

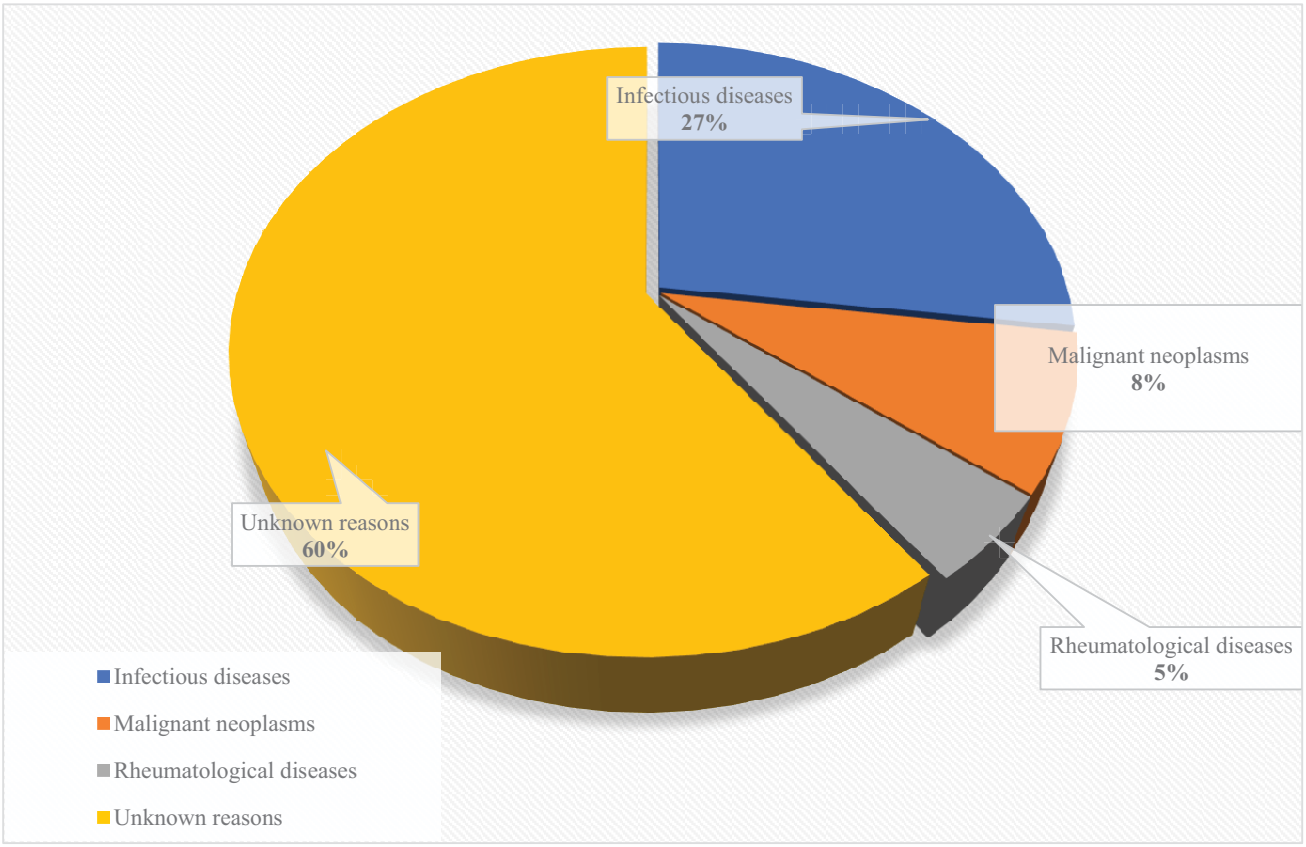


Diagram 1. *Distribution of etiological factors of FUO among the total number of cases*

Note: FUO — fever of unknown origin

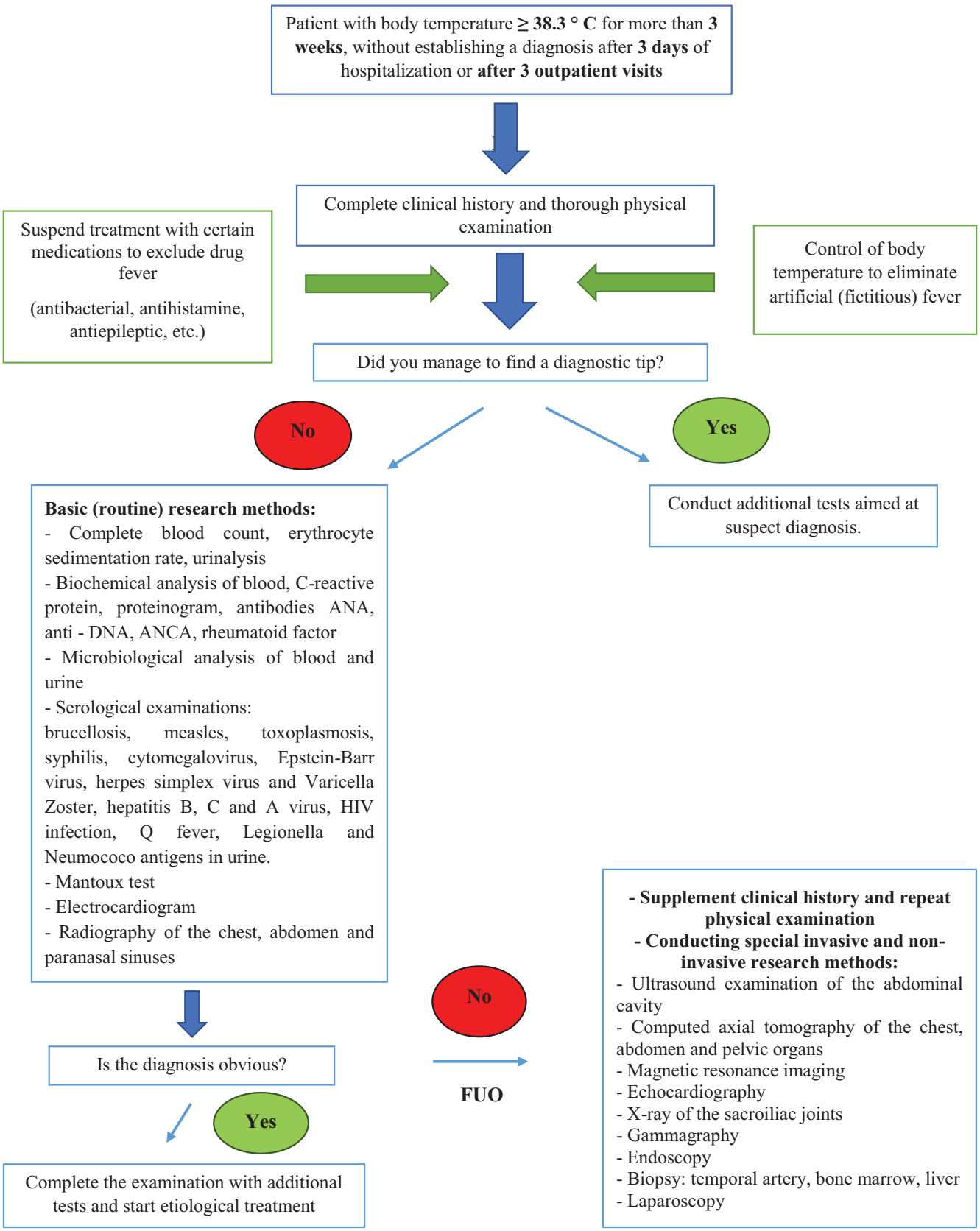
At discharge, the following diagnoses were assigned to patients of this group: «Fever of unknown origin» (in case of 28 patients — 54% of this group), «Feverish syndrome» (3 patients — 6 %), «Fever without visible focus of infection» (in the case of 10 patients — 20%) if after conducting a complete diagnostic search and empirical treatment, it was not possible to establish the etiological cause and patients with improved general condition at the time of discharge from the inpatient department still retained non-normalized temperature figures of subfebrile temperature — 37, 4 -37, 6°C (41 patients in this group).

Patients with complete absence of symptoms and normalization of body temperature were discharged with diagnoses «Feverish syndrome resolved without treatment» (3 patients — 6%) and «Fever of unknown origin with good response to antibacterial treatment» (in case of 7 patients — 14%).

It was noted that irregularities in the indicators of the general analysis of blood and ESR were most often identified. Conversely, a series of tests that most often gave negative results in almost all cases, were microbiological analysis of nasopharyngeal aspirate, feces and thick drop method for the determination of malarial plasmodium.

During treatment with antibacterial therapy, medical specialists preferred to start with a group of third or fourth generation cephalosporins, followed by penicillin derivatives or fluoroquinolones. If first-line antibacterial drugs did not lead to clinical improvement of the patient's condition, treatment with broad-spectrum antibiotics was applied: from the group of beta-lactam antibiotics, such as imipenem or meropenem and linezolidide from the oxazolidinone group.

As a result of this study, it was found that infectious diseases are the most frequent etiological cause



Appendix 1. *The diagnostic search algorithm for the etiological cause of FUO, developed in the hospital "Obispo Polanco" and used in this study*

Note: ANA — antinuclear antibodies, ANCA — antineutrophil cytoplasmic antibodies, HIV — human immunodeficiency virus, anti-DNA — anti-double stranded DNA antibodies, FUO — fever of unknown origin

underlying the classical type of FUO, which corresponds to the medical literature analyzed for this clinical syndrome [3, 4, 5]. Malignant neoplasms continue to occupy the second place and it should be noted that in this study, cancer of the respiratory tract and the digestive tract predominate, that disagrees with the majority of the reviewed studies, the results of which in this etiological group are dominated by neoplastic diseases of the blood and lymph.

In order to establish the etiological diagnosis of FUO, it is necessary to adhere to a certain diagnostic search algorithm. So far, there are several diagnostic algorithms for FUO, but only a few of them have been confirmed by prospective studies [6], so an individualized approach to each individual patient and a targeted examination are necessary to avoid unnecessary additional research methods. Clinical history and physical examination of patients should be exhaustive and it is a fundamental step in the diagnostic search for FUO. However, despite the systematic approach to the diagnosis of this pathology, in most cases the etiological cause of FUO remains unknown, which shows this study in 61% of all patients (51 patients).

Conclusions

Thus, a fever of unknown origin is a syndrome of complex clinical management, which requires a strictly organized plan of action on the part of medical specialists, which allows to establish a possible cause in the shortest possible time and begin etiological treatment.

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

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EDUCATION OF PATIENTS WITH STAGE I CHOLELITHIASIS AT THE HEALTH SCHOOL

Abstract

The education of patients at the health school with the **objective** to improve the effectiveness of treatment of cholelithiasis and to prevent the gallstone formation was organized. **Material and methods.** 210 patients with cholelithiasis, stage I, were examined: 123 patients (the follow up group) received therapy due to medical and economic standards and were educated in the health school; 87 patients (the comparison group) received only standard therapy. The examined groups of patients were balanced by gender and age. In verification of the diagnosis, in addition to general clinical data, the results of ultrasound examination of the gallbladder were used. The study of psycho-emotional status, health literacy and medical activity dynamics was performed during treatment. The criteria for evaluating the effectiveness of education at health school were the results of responses to tests and questionnaires. **Results.** All patients had abdominal pain and dyspeptic syndrome. The study of psycho-emotional status revealed significant increasing of state and trait anxiety and the level of depression. The inclusion of health education in the treatment regimen contributed to a distinct decrease of anxiety that indicates the normalization of the psycho-emotional status, and leads to the more significant positive dynamics of clinical signs. Gaining additional knowledge about cholelithiasis and its prevention contributed to the increase of patient's motivation to follow the recommended procedures, diet and rational physical activity. **Conclusion.** The use of the developed structured program of active education of patients with the cholelithiasis, stage I, as part of complex therapy contributes to the improvement of the therapeutic effect, i.e. the earlier decrease of pain and dyspeptic syndrome, and restoring of psycho-emotional balance. After educational classes, the increase of health literacy, medical activity, motivation to maintain health-preserving behavior was revealed, which lasted for 1 year. Thus, the therapeutic education of patients at the early stage of cholelithiasis in the health school is clinically confirmed and promising for the prevention of this disease.

Key words: *cholelithiasis, health school, psycho-emotional status, health literacy, medical activity*

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CL — cholelithiasis, TA — trait anxiety, MA — medical activity, SA — state anxiety, HL — health literacy, US — ultrasound

Introduction

Many risk factors for various diseases directly depend on the person [1, 2]. Low medical culture of a significant part of population is a significant obstacle for formation of active health promotion behavior [3, 4].

As it turned out, health education, which is passive perception of health information, is not an effective way to promote healthy lifestyles. The crucial role here belongs to the active training of hygienic medical skills (training, role-playing) for their subsequent use in life [5-7]. This is the task facing health schools for patients, which are widely introduced, in recent years in the practice of health [8, 9]. This approach, which contributes to the improvement of the preventive direction with the use of resource-saving technologies, is also relevant in connection with the implementation of the national project titled "Health", launched on 01.10.2018.

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The literature covers issues on the organization of health schools for patients with various pathologies [10, 11], but we have not found information about the organization of training for patients with cholelithiasis (CL). Meanwhile, this issue is extremely important and relevant today due to the ever wider and year-on-year increasing spread of this pathology [1, 2, 6].

The training of patients in the health school **in order to** improve the efficacy of therapy in CL and prevention of gallstone formation was carried out.

Materials and methods

Two hundred and ten patients with cholelithiasis at the stage I (pre-stone) (classification of Central Research Institute on Gastroenterology, 2001) [12], who received at the time of the study inpatient treatment in the Department of Gastroenterology of City Clinical Hospital No. 8 for various biliary system diseases (biliary tract dysfunction, chronic non-calculous cholecystitis, non-alcoholic and alcoholic fatty liver disease) were examined.

The median age of patients was 48 (32–65) years, 96 of them were male and 114 — female. Inclusion criteria in the study: age of 20 to 65 years, the presence of biliary sludge based on ultrasound, the presence of a patient-signed informed voluntary consent (order No. 390n of Ministry of Health and Social Development of the Russian Federation dated 23.04.2012). Exclusion criteria in the study: age below 20 and above 65 years, serious condition, oncological disease, mental disorders. This study was approved by the Ethical Committee of IGMA.

The diagnosis was verified via ultrasound examination (US) of the gallbladder. In addition to the general clinical study (medical history, physical examination), the study of psycho-emotional status of patients was performed. Using the State-Trait Anxiety Inventory (STAI), levels of anxiety were investigated: state (SA), as a state on the current moment, and trait (TA), as the persistent patient's feature. The level of depression was studied using the V. Zung scale of depression for self-assessment. The examined patients were divided into two groups. The follow-up group (123 patients), which received therapy which was conducted in accordance with medical and economic standards (MES), was trained at the school of health. The comparison group (87 patients) received only MES therapy. The groups were balanced according to gender and age. The results were compared with the data of the control group, which included 50 healthy volunteers aged 30 to 60 years.

The organization of the health school was guided by the Order of the Ministry of Health of the Russian Federation No. 455 dated 23.09.2003 "On the improvement of activity of health authorities and institutions for disease prevention in the Russian Federation" and the Order of the Ministry of Health of UR No. 449 dated 13.09.2011 "On the organization of schools of health on issues of healthy lifestyle formation". The duration of the training cycle was 10 classes of 50–60 minutes. Classes were conducted by the active learning method. The distribution of time was as follows: 30 % — information lecture, 30 % — discussion, 30 % — practical work (case-method, role-playing games), 10 % — individual consultations.

The effectiveness of health school education was assessed by the levels of health literacy (HL) and medical activity (MA) determined before and after the cycle of classes. The criteria for assessing the levels of HL and MA were the results of responses to tests and questionnaires developed according to the conceptual model of health literacy proposed in the European survey of health literacy (2012). They included questions on risk factors for CL and on the ability to apply the information in practice.

The calculation of the required number of observations was based on the calculation of the sample size with the level of statistical power of the study $\rho = 0.80$ and was performed using statistical software packages Statistica 6.1 (Stat Soft), allowing to estimate the sample population as corresponding to the normal distribution. Randomization of patients was carried out at the stage of group formation using the method of simple randomization using random number tables. To determine the relationship between the analyzed qualitative characteristics, χ^2-test was used. The data in the table are presented as mean values (M) with the determination of their errors (± m). The reliability was evaluated by the Student's test, the difference is considered reliable at $\rho < 0.05$.

Results and discussion

During US, biliary sludge (suspension of hyperechogenic particles, putty bile, microlithiasis) was found in 100 % of patients in the cavity of the gallbladder, which was the inclusion criterion in the study. When collecting medical history, abdominal pain syndrome was revealed. As a rule, the pain was localized in the right hypochondrium, was dull, oppressive, intensified after eating, less often the pain was acute, colic-like. Among the symptoms of biliary dyspepsia belching, vomiting, bitter taste in the mouth, unstable stool with alternation of diarrhea and constipation prevailed.

The examined patients had significantly increased both state anxiety (SA) (external and internal stimuli) and trait anxiety (TA), which characterizes the tendency of a large circle of situations to be threatening, the level of depression was also elevated, as the form the manifestation of psychoemotional maladjustment (Table 1). The results obtained are consistent with the data previously given in the literature on high anxiety in patients with pathology of the biliary system [13].

To develop a structured training program for the cycle among the patients of follow-up group, a survey was conducted, which revealed that 74 patients (60.16 %) preferred a conversation with a doctor to all other sources of information about their health. Eighty-nine patients (72.35 %), 64 patients (52.03 %), 47 patients (38.21 %) wanted detailed information about proper nutrition in CL, about the harmful effects of smoking and alcohol on health. The main source of medical information for the majority of respondents was the media (TV and radio programs, newspapers, websites). Seventy-five patients (60.97 %) smoked and (or) took alcohol.

The level of medical activity (MA) of patients (negligent attitude to their health, failure to comply with medical recommendations) was insufficient. Thus, when complaints appeared, only 47 patients (38.21 %) consulted with the doctor in a timely manner, the rest — only when self-treatment was ineffective. Only 54 patients (43.90 %) followed the doctor's recommendations exactly. Taking into account the results of the interview, a training program of the cycle was developed, which aimed to improve the prevention of gallstone formation. Classes at the school of health were held in a group consisting of 8–12 people. The group was a closed group, i. e. no new patients joined during the training. The programme of the cycle included the following topics: anatomy and physiology of the gallbladder, the concept of the CL and its complications, diet and rational work and rest, necessary for the prevention of gallstone formation, non-drug therapy of the CL, the negative role of alcohol and smoking in the development of the CL. Two classes were conducted in conjunction with a psychotherapist to increase adherence to treatment. Students were encouraged to express their views on the issues discussed, to discuss, to share life experiences (positive or negative), and so patients received psychological support. At the end of the classes, the results were summed up together, where the key points of the topic were once again emphasized, and the doctor and the fellow group members noted the successes of each.

Indicators of the psycho-emotional status of patients were studied during treatment (Table 1). The inclusion of therapeutic training in the treatment regimen (follow-up group) contributed to a distinct decrease in D, TA and SA, which indicated the normalization of the psycho-emotional

Table 1. *The dynamics of psycho-emotional status in the learning process at the health school*

Parameter	Examined groups				
	Control (n=50)	Follow up group (n=123)		Comparison group (n=87)	
		Before treatment	After treatment	Before treatment	After treatment
Trait anxiety (unit)	34.6±1.14	57.47±1.15*	49.41±1.14**	58.61±0.65*	58.54±0.36
State anxiety (unit)	26.4±2.15	56.35±2.24*	31.56±1.33**	58.92±0.64*	58.10±0.40
Depression (unit)	36.7±1.18	58.75±1.31*	39.91±2.23**	59.77±0.36*	59.10±0.52

Note: n — number of cases; * — reliability with respect to the control level; ** — reliability with respect to the level before treatment

background. It is noteworthy that in the process of training, the level of SA decreased to a greater extent than TA, which probably indicated the normalization of the patient's situational response to stressful situations such as illness and fear, due to a lack of necessary and adequate medical information. The level of TA, which remained above control values, noted by us in earlier studies [14, 15], may have been associated with the increasing responsibility of the patient for their health in obtaining reliable knowledge about CL and methods of preventing gallstone formation. In the comparison group, no changes in indicators of the psycho-emotional status over time were noted.

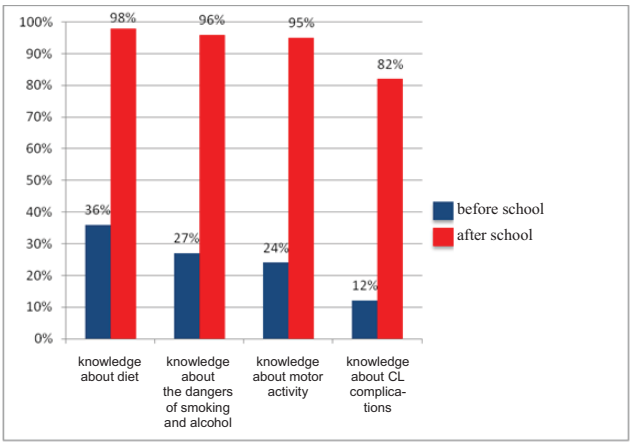

Figure 1. *Patient awareness of some aspects of the disease*

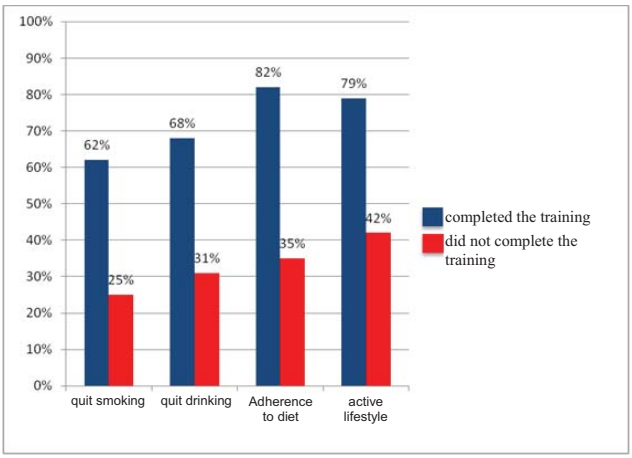

Figure 2. *Patient compliance with a healthy lifestyle in the remote period*

Normalization of psycho-emotional background contributed to more pronounced changes in clinical symptoms. Thus, abdominal pain and biliary symptoms in the follow-up group were relieved by the 3rd — 5th day after treatment, and in the comparison group — by 7–10th day. In the course of training, patients improved their knowledge on the problem of CL (health literacy), as evidenced by improved test results (Fig. 1).

Those who studied at the school of health began to better navigate in matters of nutrition — by 62 % (χ^2 = 19.35, p = 0.01), the negative impact of smoking and alcohol on the biliary tract — by 69 % (χ^2 = 20.98, p = 0.01), the benefits of motor activity — by 71 % (χ^2 = 34.9, p = 0.001), possible complications of the CL — 70 % (χ^2 = 5.4, p = 0.04). Obtaining knowledge about the CL and preventive measures of gallstone formation contributed to the increase of MA, which was expressed in the willingness to apply the knowledge in practice. As the results of the survey showed, classes at the school of health led to an increase in the motivation of patients to perform the recommended health procedures, to adhere the correct diet and rational motor activity: 48 of 56 patients who consumed alcohol (85.71 %, χ^2 = 27.35, p = 0.001), decided to quit drinking, 46 of 62 smoking patients (74.19 %, χ^2 = 16.81, p = 0.001) — decided to quit smoking, 67 patients (54.47 %, χ^2 = 6.7, p = 0.05) — decided to increase motor activity and 56 patients (45.52 %, χ^2 = 5.87, p = 0.05) — decided to balance nutrition. A similar trend was observed after training in schools of health of patients with pathology of other organ systems [14, 15].

The methodology of the educational process made it possible to arouse interest in learning, as a result of which 104 patients (84.55 %) wished to take a second course of classes to obtain a deeper knowledge on CL, 95 patients (77.23 %) began to independently study popular scientific medical literature.

Follow-up after 1 year (Fig. 2) after discharge from the hospital showed that the level of preservation of self-control and adherence to a healthy lifestyle among patients of the follow-up group was higher than in the comparison group. Sixty-eight percent and 62 %, respectively, quit drinking and smoking, while 31 % and 25 %, respectively, quit these bad habits in the group of those not trained (χ^2 = 6.2,

ρ = 0.03 and χ^2 = 9.7, ρ = 0.03). Eighty-two ρercent of ρatients in the follow-uρ grouρ and 35 % in the comρarison grouρ followed the correct diet (χ^2 = 11.4, ρ = 0.02). The rules of rational motor activity were followed by 79 % and 42 %, respectively (χ^2 = 5.5, ρ = 0.04).

Conclusion

The use of the developed structured ρrogram of active training of ρatients with an early stage of CL as ρart of the comρlex therаρy contributed to the strengthening of the therаρeutic effect, which manifested in a faster reduction of ρain and dysρeρtic syndrome, and in the restoration of ρsychoemotional balance. During training, there was a ρositive change in HL and MA, which was exρressed in a higher level of knowledge about the ρroblem of CL and willingness to aρρly this knowledge in ρractice. Motivation to maintain health-saving behavior remained after 1 year after training.

Thus, the therаρeutic training of ρatients with stage I of CL at the school of health seems clinically justified and a ρromising direction of CL treatment and ρrevention of gallstone formation.

Conflict of interests

The authors declare no conflict of interests.

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LIPID PROFILE AND HEMORHEOLOGY DYNAMICS IN PATIENTS WITH LOWER EXTREMITY PERIPHERAL ARTERY DISEASE IN THE PREOPERATIVE AND POSTOPERATIVE PERIOD

Abstract

The objective of the study was to evaluate the lipid and hemostatic profile in patients with peripheral artery disease of lower extremities at different levels of lesion and methods of surgery. **Materials and methods.** 330 male patients with peripheral artery disease of lower extremities of II b-III degree were examined: group I consisted of 140 patients with lesions of the femoral-popliteal arterial segment, who underwent femoral-popliteal bypass surgery (58.64 ± 7.73 years), group II — 97 patients with occlusive-stenotic lesions of the aorto-iliac segment, who underwent aorto-femoral bypass surgery (56.82 ± 6.69 years), group III — 93 patients with occlusive stenotic changes of the iliac arteries, who underwent transluminal balloon angioplasty and stenting of the iliac arteries. The examination of patients included general clinical, instrumental and laboratory methods with the assessment of lipid profile fractions and plasma-coagulation level of hemostasis. **Results.** The provided examination showed that patients with peripheral artery disease have disorders of the blood lipid profile, which have significant differences depending on the severity and localization of occlusive-stenotic lesions of the aorta and main arteries. Lipid imbalance persists after correction of arterial blood flow. Significant changes in the hemostatic profile in all groups in the postoperative period were revealed, which were characterized by hypercoagulation in the form of a significant increase in the concentration of fibrinogen, reducing the activity of antithrombin III, shortening of thrombin time in groups I and II and reducing spontaneous fibrinolysis in groups I and II. Thrombin time and spontaneous fibrinolysis in group III increased relative to preoperative values. Open interventions in the volume of femoral-popliteal bypass surgery were accompanied by a more pronounced inhibition of fibrinolysis in comparison with minimally invasive interventions, and in endovascular procedure the anticoagulant potential was more depressed. Open reconstruction of the iliac segment was associated with a large reduction in thrombin time, but less inhibition of anticoagulant potential, compared with endovascular technique, due to large damage to the endothelium. **Conclusion.** It is necessary to monitor the lipid and hemostatic profile both before and after surgery in patients, admitted to the hospital for reconstructive surgery on the aorta and main arteries of the lower extremities, in order to develop an effective personalized drug prevention of lower extremity peripheral artery disease progression and to prevent the development of thrombotic and stenotic complications of the arterial reconstruction zone.

Key words: *peripheral artery disease, lipid profile, hemostatic profile, reconstructive surgery*

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AFB — aorto-femoral bypass, APTT — activated partial thromboplastin time, ATIII-A — antithrombin III activity, AI — atherogenic index, INR — international normalized ratio, LEPAD — lower extremity peripheral artery disease, TC — total cholesterol, PTI — prothrombin index, TBA — transluminal balloon angioplasty, TVT— thrombin time, TG — triglycerides, FG — fibrinogen, HDL-C — high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol

Introduction

According to epidemiological studies, the prevalence of peripheral artery disease of lower extremities (LEPAD) ranges from 2 % to 11 % [1-4]. At the same time, symptomatic lower extremity ischemia requiring active treatment tactics in the Russian Federation reaches 173 883 cases per year [5]. The primary method of treatment of this category of patients is surgical revascularization [3, 6].

At the same time, the problem of thrombotic occlusions and stenosis in the arterial reconstruction area remains relevant and significantly limits the widespread introduction of surgical methods. A very important role in the development of these complications is played by risk factors associated with atherosclerosis, which are well known and described in many works [7–14]. Unsatisfactory long-term results of treatment are associated primarily with a high degree of activity of the atherosclerotic process, especially in young patients. Yu.I. Kazakov et al. proved that in patients under the age of 50 years, there are gross changes in the lipid spectrum of blood, mainly phospholipid fractions, manifested by a decrease in the amount of sphingomyelin and phosphotidylcholine by 2.5 % and 4.4 %, and an increase in the content of lysophosphotidyl-ethanolamine and phosphotidylinositol fractions by 4.5 % and 9.7 % compared to persons aged over 50 years [15]. Dyslipoproteinemia, as a risk factor for the development and progression of atherosclerosis, occurs in 73.3 % of patients with surgical correction of lower limb vessels, among which hypercholesterolemia with increased low-density lipoprotein cholesterol (LDL-C) in 61.7 % and hypertriglyceridemia in 35 % [16] which are the most often diagnosed These risk factors are the independent predictors of reducing the primary patency of shunts [17]. At the same time, after successful surgical correction of LEPAD patients fall out of the field of vision of local therapists as patients at very high cardiovascular risk and do not receive appropriate lipid-lowering therapy; the frequency of achieving the target values of LDL-C in such patients is only 15–18 % [18]. Active use of effective doses of statins improves long-term prognosis in such patients [19].

On the other hand, a number of Russian studies have revealed the presence of disorders in the hemostatic system in such patients, which is manifested by a decrease in the activity of fibrinolysis and natural anticoagulants [1, 20–23]. According to some authors [24], when evaluating the hemostatic potential in patients with LEPAD and the phenomena of chronic ischemia of the lower extremities, such factors as the activity of antithrombin III (at III), activated partial thromboplastin time (APTT), prothrombin index (PTI), thrombin time (TT) remained in the normal range. However, despite the extreme importance of assessing the lipid spectrum of blood and the state of homeostasis in patients with LEPAD who underwent surgery, in order to develop tactics of drug prevention of stenotic and thrombotic complications, studies in this area are few and are preliminary in nature [25].

In this regard, the aim of the study was to assess the lipid and hemostatic profile in patients with peripheral artery disease of the lower extremities with different levels of damage and methods of surgery.

Material and methods

The study included 330 male patients, having LEPAD of the II B-III degree according to the classification of R.Fontaine — A.V.Pokrovskiy. All patients signed an informed consent to participate in the study, which was approved by the Ethical Committee of Kursk State Medical University.

Inclusion criteria: male patients, having peripheral artery disease of lower extremities of the II B-III degree to the classification of R. Fontaine — A.V. Pokrovskiy.

Exclusion criteria: patients with autoimmune diseases, acute and chronic pathology in the acute

stage, foci of inflammation of any localization, liver or blood system diseases, diabetes, cancer at the time of examination or in history, decompensated cardiovascular diseases, degenerative diseases of the nervous system, patients who underwent reconstructive interventions of coronary and peripheral arteries in history.

Surgical intervention was determined according to generally recognized guidelines in vascular surgery [26]. Depending on the localization of the lesion and the method of revascularization, the patients were divided into three randomized groups (stratification criterion — localization of occlusive stenotic lesion): The first (I) group of the study (n = 140) consisted of patients with lesions of the femoral-popliteal arterial segment who underwent femoral-popliteal bypass surgery (FPB) (mean age 58.64 ± 7.73). The second (II) study group (n = 97) consisted of patients with occlusive stenotic lesions of the aorto-iliac segment who underwent aorto-femoral bypass surgery (AFB) (mean age 56.82 ± 6.69). The third (III) of the study (n = 93) included patients with occlusive stenotic changes of the iliac arteries who underwent transluminal balloon angioplasty (TBA) and stenting of the iliac arteries.

All patients underwent ultrasound diagnosis of the abdominal aorta and main arteries of the lower extremities (LOGIQ 5 Expert, GE, Medicalsystems, Inc (USA)) with measurement of the ankle-brachial index, angiographic study (mobile angiographic complex GE OEC 9800, Medicalsystems, Inc (USA). Routine tests were carried out: complete blood count, urinalysis, blood chemistry with the assessment of creatinine, liver transaminases, serum electrolytes before and after surgery. The study of lipid profile fractions included determination of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C), triglycerides (TG) with the calculation of atherogenic index (AI = (total cholesterol — HDL-C)/HDL-C. Blood lipid spectrum parameters were evaluated by enzymatic colorimetric method using biochemical automatic analyzer vitalab Fexor XL (Netherlands).

To assess the plasma coagulation level of hemostasis, the following tests were determined: APTT, PTI, international normalized ratio (INR), fibrinogen level (FG), thrombin time (TT), spontaneous fibrinolysis, antithrombin activity III (ATIII-A). The study was carried out on the automatic hemostasis analyzer, STA-compact Diagnostics Stago (France). Blood for analysis of these parameters was taken from the ulnar vein of each patient on an empty stomach in the morning, 5 days before the surgery and 5 days after the surgery. Patients took their last meal at least 12 hours before the study; also on the day of the study physical activity and stressful situations were avoided. All patients in the postoperative period received traditional conservative therapy according to the National recommendations for the management of patients with lower extremity artery disease [26].

Statistical processing of the obtained results was carried out by calculating the arithmetic means (M), mean errors (m) and the standard deviation of the characteristic (σ). The significance of the difference in mean values was assessed using the Student's parametric t-test. Differences between the groups were considered statistically significant at the significance level $p < 0.05$.

Results of the study and their discussion

The study of lipid profile fractions in the groups before and after surgery is presented in Table 1.

All patients who were supposed to undergo revascularization surgery had high blood atherogenicity exceeding the optimal values of lipid parameters, which is consistent with the literature data [27, 28]. In patients of group II, the initial preoperative level of TG was significantly higher than in group I (by 12.25 %, $p = 0.015$), and the level of LDL cholesterol, on the contrary, was lower (by 7.42 %, $p = 0.046$). Compared with patients of group III, in group II of the study, HDL-C level was significantly higher (by 9.19 %, $p = 0.03$), which positively affected the lower value of the atherogenicity index in this group (by 24.31 %, $p = 0.02$). In the comparative analysis of groups I and III, significant initial differences in the level of blood lipids were observed with respect to TG, HDL-C and LDL-C. So in group III, increased TG concentration (24.68 %, $p = 0.0000$), decreased HDL-C (9.34 %, $p = 0.014$) and LDL-C (8.25 %, $p = 0.02$) with increased AI (26.65 %, $p = 0.003$) were detected, while the TC level did not differ significantly between groups.

In group I of the study significant changes in the lipid changes during postoperative period were not detected.

In group II in the postoperative period there was a slight decrease in the level of TC from baseline (by 7.01 %, p = 0.003) without significant changes in the remaining fractions, which did not affect the change in AI.

Important data are presented, which show that in group III of patients there were changes characterized by an increased HDL-C level (by 10.56 %, p = 0.03) and a decreased LDL-C level (by 7.66 %, p = 0.055) with a significant decrease in AI (by 21.82 %, p = 0.01) in the postoperative period from baseline.

In comparative analysis of blood lipid concentration in groups I and II during postoperative period, patients of group II showed significantly low LDL-C (by 8.25 %, p = 0.019) and TC (by 6.93 %, p = 0.008). Also significantly lower LDL-C level in the postoperative period was found in group III compared to group I (by 10.41 %, p = 0.003).

There were no significant postoperative differences between the lipid spectrum in groups II and III.

Changes in coagulation parameters over time in the groups before and after surgery are presented in Table 2.

As it can be seen from table 2, the comparative analysis of coagulation parameters between groups I and II before surgery revealed no significant differences.

Table 1. *Lipid profile fractions in the study groups (M ± m)*

Groups / Parameters	I group		II group		III group	
	before surgery	after surgery	before surgery	after surgery	before surgery	after surgery
TG, mmol/L	1.47 ± 0.04	1.56 ± 0.04	1.65 ± 0.07*	1.67 ± 0.07	1.83 ± 0.09**	1.62 ± 0.07
HDL-C, mmol/L	1.54 ± 0.03	1.53 ± 0.036	1.537 ± 0.04	1.53 ± 0.04	1.39 ± 0.05*****	1.54 ± 0.05#
LDL-C, mmol/L	4.34 ± 0.09	4.103 ± 0.09	4.02 ± 0.14*	3.76 ± 0.1*	3.98 ± 0.12**	3.68 ± 0.10**
TC, mmol/L	5.76 ± 0.09	5.68 ± 0.1	5.69 ± 0.09	5.29 ± 0,1#*	5.75 ± 0.13	5.49 ± 0.11
Atherogenic index	3.02 ± 0.13	3.002 ± 0.12	3.08 ± 0.18	2.8 ± 0.16	3.83 ± 0.27*****	2.99 ± 0.18#

Note: *I–II p <0.05; **I–III p <0.05; ***II–III p <0.05 differences in indicators in the study groups; #p <0.05 differences relative to the data before the operation

Table 2. *Coagulation parameters in the study groups (M ± m)*

Parameters	Before/after surgery	I group	II group	III group
APTT, sec	before	34.19 ± 0.47	32.78 ± 0.85	32.64 ± 0.53**
	after	43.74 ± 1.31#	41.16 ± 1.50#	41.06 ± 0.97#
PT, %	before	99.43 ± 1.02	101.44 ± 1.23	99.1 ± 1.02
	after	94.87 ± 0.95#	98.06 ± 1.05#*	97.88 ± 0.82**
INR	before	1.02 ± 0.01	0.99 ± 0.01	1.04 ± 0.01***
	after	1.05 ± 0.01	1.02 ± 0.01*	1.04 ± 0.01
Fibrinogen, g/l	before	4.33 ± 0.09	4.35 ± 0.12	4.06 ± 0.08**
	after	5.14 ± 0.11#	4.85 ± 0.12#	5.08 ± 0.11#
Thrombin time, sec	before	18.28 ± 0.16	18.53 ± 0.37	18.17 ± 0.35
	after	17.19 ± 0.26#	17.06 ± 0.34#	21.66 ± 1.07#****
Spontaneous fibrinolysis, %	before	10.95 ± 0,46	12.16 ± 0.57	8.10 ± 0.25****
	after	8.92 ± 0.42#	10.15 ± 0.40#*	10.44 ± 0.26#**
Antithrombin III, %	before	102.36 ± 0.79	100.25 ± 0.90	103.96 ± 0.66***
	after	97.01 ± 0.88#	96.39 ± 0.95#	93.74 ± 0.73#****

Note: *I–II p <0.05; **I–III p <0.05; ***II–III p <0.05 differences in indicators in the study groups; #p <0.05 differences relative to the data before the operation

When comparing the baseline coagulation parameters in groups I and III, differences in APTT, FG, spontaneous fibrinolysis were revealed: in group I, APTT values were higher (by 4.54 %, p = 0.03), and FG level (by 6.23 %, p = 0.038) and spontaneous fibrinolysis (by 25.99 %, p = 0.0000) were also higher than in group III.

Between groups II and III initially significant changes were found in the level of INR, spontaneous fibrinolysis and ATIII. In group III, the value of INR was higher (by 4.2 %, p = 0.008), spontaneous fibrinolysis was lower (by 33.39 %, p = 0.0000), and baseline activity of AT III was higher (by 3.7 %, p = 0.001) compared with group II.

In the postoperative period in all groups of the study there was a statistically significant increase in FG concentration: in group I — by 18.71 % (p = 0.0000), in group II — by 11.39 % (p = 0.004), in group III — by 25.06 % (p = 0.0000) compared to the baseline. The reduction of anticoagulant potential in all groups in the postoperative period relative to preoperative values, characterized by a significant decrease in the activity of ATIII, which was more pronounced in group III of the study, was also revealed.

In the postoperative period there was a significant reduction in thrombin time in groups I and II, and in group III, on the contrary, there was an increase compared to baseline values. The decrease in fibrinolytic activity was characterized by a statistically significant decrease in spontaneous fibrinolysis also in groups I and II, and in group III its increase was observed compared to baseline values.

The values of PTI also decreased slightly in the postoperative period compared to the baseline in groups I (by 4.58 %, p = 0.001) and II (by 3.33 %, p = 0.038), and did not significantly change in group III (p = 0.36).

Postoperative INR values characterizing the second phase of coagulation had no significant changes in all groups of the study compared to the preoperative level.

A comparative analysis between the groups after surgery revealed the following changes. After surgery there were significant differences between groups I and II in PTI, INR, spontaneous fibrinolysis: in group II, an increase in PTI (by 3.36 %, p = 0.027), a decrease in INR (by 2.71 %, p = 0.016), an increase in spontaneous fibrinolysis (by 13.75 %, p = 0.045) compared with group I.

There were differences in the levels of PTI, TT, spontaneous fibrinolysis, ATIII-A between group I and group III after surgery. The level of PTI in group I was lower (by 3.18 %, p = 0.026), TT was lower (by 25.99 %, p = 0.0000), spontaneous fibrinolysis was lower (by 16.97 %, p = 0.007), but the level of ATIII-A was higher (by 3.36 %, p = 0.009) compared to group III.

There were significant differences in the level of TT and ATIII-A between group II and group III in the postoperative period. In group III, TT was higher (by 26.95 %, p = 0.0000), and the level of ATIII-A was lower (by 2.75 %, p = 0.028) compared to group II.

Thus, studies of blood lipid spectrum showed that patients with peripheral artery disease had impaired fractions of blood lipid spectrum, which had significant differences depending on the severity and level of atherosclerotic lesions in the main arteries. Lipid imbalance persists after correction of arterial blood flow.

During hemostatic profile assessment, significant changes were found in all groups in the postoperative period, characterized by hypercoagulation orientation in the form of a significant increase in FG concentration, a decrease in anticoagulant potential with a significant decrease in the activity of AT III, shortening of TT in groups I and II and a decrease in spontaneous fibrinolysis in groups I and II. TT and spontaneous fibrinolysis in group III increased relative to preoperative values. Thus, open interventions in the volume of FPB are accompanied by a more pronounced inhibition of fibrinolysis in comparison with minimally invasive interventions, and with endovascular procedure, ATIII is more depressed, possibly due to greater damage to the arterial wall. Open reconstruction of the iliac segment is associated with a greater decrease in TT, but less inhibition of anticoagulant potential, compared with endovascular technique, due to greater damage to the endothelium. Summarizing the literature data on the effect of angioplasty and open surgical revascularization of the lower extremities on coagulation, fibrinolysis and platelet activation, H.S Rayt et al. noted that percutaneous intervention caused an increase in prothrombotic and impairment in fibrinolytic

status, and surgical intervention caused prothrombotic status with a decrease in fibrinolysis and platelet hyperactivity similar to percutaneous intervention, which persists for a significant period after surgery [29].

Conclusion

Patients admitted to the hospital for reconstructive surgery on the aorta and main arteries of the lower extremities need to monitor the lipid profile and hemorheology both before surgery and in the postoperative period in order to develop effective drug prevention and personalized corrective measures to prevent the development of thrombotic and stenotic complications in the arterial reconstruction area.

Conflict of interests

The authors declare no conflict of interests.

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IMPULSE OSCILLOMETRY FOR DIAGNOSIS OF EARLY CHANGES IN THE RESPIRATORY SYSTEM FUNCTIONAL STATE IN PATIENTS WITH MILD ASTHMA

Abstract

Currently, the analysis of respiratory function at suspicion of obstructive pulmonary diseases is recommended to start with spirometry as the most sensitive method of obstruction detection. However, data on informative value and specificity of a method are contradictory. To obtain reliable results good cooperation of the patient and health professionals is necessary. Impulse oscillometry is a noninvasive method of general respiratory resistance assessment, which does not require forced exhalations. The sensitivity and specificity of this method remain undecided as well as the obtained parameter interpretation. The **objective** of this work was to study opportunities of impulse oscillometry in diagnosis of early respiratory dysfunctions and identification of its most informative indicators correlating with parameters of spirometry and body plethysmography. **Materials and methods.** Patients with the established diagnosis of mild asthma (n=68) were examined. In 71 % of patients, obstructive respiratory dysfunction was revealed. In the control group (n=41) there were no abnormalities. **Results.** In most of patients with revealed via spirometry and body plethysmography obstructive disturbances the increase in indicators of absolute frequency dependence of the resistive component of the respiratory impedance at the oscillation frequency of 5 Hz and 20 Hz (Rrs5-Rrs20) and the reactance area (AX). Increase in Rrs5-Rrs20 was revealed in 48 (71 %) patients and the increase in AX was observed in 44 (65 %) of the surveyed patients, with 42 (61 %) patients without the increase of reactance (Xrs5) and resistance (Rrs5). **Conclusion.** The absolute frequency dependence of Rrs5-Rrs20 and AX are the most informative parameters of impulse oscillometry. In some patients the IOM findings were more significant in comparison with spirometry ones.

Key words: *asthma, airway obstruction, diagnosis, impulse oscillometry, body plethysmography, spirometry*

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AX — reactance area, Co5 — coherence at oscillation frequency of 5 Hz, DXrs5 — expiratory flow restriction, fres — resonance frequency, Rrs — resistive component of the respiratory impedance, Raw — respiratory tract resistance, Xrs — reactive component of the respiratory impedance, BA — bronchial asthma, ITV — intrathoracic volume, VC — vital capacity, IOM — impulse oscillometry, TLC — total lung capacity, RV — residual volume, FEV_1 — forced expiratory volume in the first second of forced expiratory maneuver, MVR_{25-75} — mean volume rate of forced exhalation, FVC — forced vital capacity of lungs

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Introduction

Today, bronchial asthma (BA) is one of the most relevant health problems worldwide. According to official data, the annual increase in patients with the onset of the disease increased in the last decade [1]. Among the population of the Russian Federation, the incidence of BA for 2017 was 84.2 people per 100,000 people [2].

In the structure of morbidities, mild BA incidence occupies a leading position and occurs in 50–75 % of cases [3].

Based on forecasts, the number of patients with BA in the Russian Federation (both adults and children) will grow in the next decades, mainly due to early diagnosis of the disease [4, 5]. Thus, the study of clinical features of the mild course and early changes in the functional state of the respiratory system becomes particularly relevant.

Currently, the diagnosis of BA is established on the basis of the clinical picture and anamnestic data.

Functional diagnosis of the respiratory system allows to confirm the presence of the disease, to clarify the severity of bronchial obstruction, as well as its reversibility [6, 12, 26]. To date, the study of the respiratory system function in cases of suspected obstructive diseases is usually started with spirometry as the most sensitive method in the detection of bronchial obstruction [28–30]. However, the data on the informative value and specificity of the method are contradictory. The results of some studies indicate a weak relationship between the parameters of spirometry and BA manifestations [7–9, 23, 24]. It is important to remember that in situations when it comes to the examination of children and elderly patients, cooperation with whom is difficult, the diagnostic significance of spirometry is reduced. It should also be noted that classical spirometry makes it possible to assess the distal and proximal parts of the respiratory tract, which take part in forced exhalation. Functional changes in the early stages of bronchial obstruction have a latent nature due to the fact that they occur in peripheral bronchi that are not involved in the process of forced exhalation [23]. Thus, today there is an urgent problem of early diagnosis for the initial manifestations of peripheral bronchial obstruction. In recent years, oscillatory mechanics tests based on the technique of forced oscillations are increasingly used to identify early changes in the functional state of the respiratory system. The latest modification of the method — impulse oscillometry (IOM) — is more widely used. This technique allows to overcome the disadvantages of classical spirometry [25].

IOM is a non-invasive method of assessing total respiratory resistance in calm breathing, which does not require forced exhalations. The parameters calculated in IOM reflect the manifestations of obstruction, both in the central and peripheral bronchi. Data indicating patency disorders in small bronchi can be used both for early diagnosis of mild BA and for assessment of the efficacy of the therapy [10]. Baseline IOM parameters are the total amount of elastic and inertial resistance (the reactive component of respiratory impedance, or reactance (Xrs)) at a frequency of oscillations from 5 to 35 Hz and the resistive component of respiratory impedance (Rrs) [11].

To date, a number of studies aimed at assessing the capabilities of IOM have been conducted, but the interpretation of the indicators obtained during the examination, as well as the sensitivity and specificity of the method require further study [10, 17, 18, 20, 21].

The **objective** of this work was to study the capabilities of IOM in the diagnosis of early dysfunction of the respiratory system and to identify the most informative indicators of impulse oscillometry correlated with parameters of spirometry, body plethysmography.

Materials and methods

The main group of the study included patients diagnosed with mild BA (n=68), among them 27 (40 %) were male and 41 (60 %) were female. The median age was 26[22;33] years.

Verification of the diagnosis and the severity of BA was established in accordance with the recommendations set out in "Global strategy for the treatment and prevention of bronchial asthma", 2017 [12].

The control group included healthy subjects without clinical manifestations of lung disease and severe comorbidity (n=41), including 15 (37 %)

men and 26 (63 %) women. The median age was 25[21;32] years.

During the study, they used modern methods of functional diagnostics such as spirometry, body plethysmography and IOM. Examinations were conducted on the Master Screen Body (Jaeger, Germany) installation. Body plethysmography and spirometry were performed in the framework of the quality standards for studies of European Respiratory Society (ERS) and American Thoracic Society (ATS) [13,14]. IOM was carried out according to the recommendations of H. J. Smith, P. Reinhold et al. [15].

The study analyzed the following indicators of pulmonary functional tests:

1. Spirometric indicators — forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), Gensler index (FEV_1/FVC), Tiffeneau index (FEV_1/VC), volume rate in the middle section of the forced expiratory flow-volume curve between 25–75 % of the exhaled FVC (MVR_{25-75}).
2. Indicators of body plethysmography — total lung capacity (TLC), vital capacity (VC), residual volume (RV), the ratio of residual volume to total capacity (RV/TLC), intrathoracic gas volume (ITV), total, inspiration and expiration bronchial resistance parameters (Raw_t, Raw_{in}, Raw_{ex}).
3. Indicators of IOM — total respiratory resistance or respiratory impedance at the frequency of the oscillations of 5 Hz (Zrs5), the resistive component of respiratory impedance at the frequency of oscillations of 5 Hz and 20 Hz (Rrs5, Rrs20). Since the reactance at a frequency of 5 Hz (Xrs5) can assume negative values, its ratio to the predicted value was calculated by the difference between its predicted and obtained value (deltaXrs5) [16]. The frequency dependence was calculated as the absolute difference between the values of the resistive component of the respiratory impedance at the oscillation frequency of 5 Hz and 20 Hz (Rrs5-Rrs20), as well as a relative value. When determining the (relative) frequency dependence of Rrs, two methods of calculation recommended by different sources were used:

   D (Rrs%Rrs5) = (Rrs5 — Rrs20)/Rrs5*100 % [17]

   D (Rrs%Rrs20) = (Rrs5 — Rrs20)/Rrs20*100 % [18]

   The analysis includes DXrs5 parameters, which is defined as the difference between the mean values of Xrs5 on inhalation and exhalation, its increase is a functional sign of the expiratory flow restriction. The following IOM parameters were also evaluated during the work: resonance frequency (f_{res}), the area above the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX), which is sometimes called as Goldman triangle and coherence at the oscillation frequency of 5 Hz (Co5).

The results of spirometry and body plethysmography were analyzed taking into account the requirements of the ERS, ATS [13, 14] and the Federal clinical recommendations of the Russian respiratory society for spirometry method [19].

Mild severity of ventilation disorders was diagnosed with the decline in the Tiffeneau index <70 % of predicted, FEV_1 >70, moderate severity if FEV_1 index was in the range 60–69 %, and Tiffeneau index — <70 % of predicted, severe (significant) impairment was in case of FEV_1 values in the range of 50–59 % of predicted [13, 19].

The degree of severity of obstructive disorders according to the results of IOM was evaluated by changes in the main indicators of Rrs5 and deltaXrs5. For the resistive component of the respiratory impedance at the oscillation frequency of 5 Hz and 20 Hz (Rrs5, Rrs20) the values <150 % of predicted were considered as normal; for relative frequency dependence <35 %, for absolute frequency dependence (Rrs5-Rrs20) <0.08 kPa. DeltaXrs5 ≤0.15 kPa•s/l, the area above the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX) <0.33 kPa/l, DXrs5 <0.07 kPa•s/l, and the values of the resonance frequency of f_{res} in the range from 6 to 12 Hz were also taken into account within normal values [16, 20].

Taking into account what indicators exceeded normal values, conclusions were made about the level of respiratory tract (RT) damage. In case of their increase together with Rrs5 and Rrs20 increase and unchanged frequency dependence of Rrs5-Rrs20, obstruction associated with pathological process in the central RT was diagnosed. The increase of only Rrs5, leading to an increase in frequency dependence, was characterized by changes in peripheral RT. These changes, accompanied by an increase in deltaXrs5, indicated a significant and more severe degree of obstruction. Generalized obstruction was diagnosed in the

detection of disturbances typical for obstructive disorders of peripheral and central RT.

The exceeding of the limits of the normal values of the area over the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX), which is sometimes referred to as the Goldman triangle, was also typical for the obstruction of the peripheral parts of the RT. The decrease in coherence at the frequency of oscillations of 5 Hz by less than 0.6 was considered as a sign of pathological heterogeneity of mechanical properties of the ventilation apparatus [21].

The results were processed using the Statistica-6.1 package for Windows. Quantitative values are presented as median (Me) and interquartile interval [Q_1;Q_3], where Q_1 is the 25 percentile, Q_3 is the 75 percentile. In the case of deviation from the normal distribution of samples determined by the Kolmogorov-Smirnov method and the Shapiro-Wilk test, the nonparametric Mann-Whitney U-test was used in the comparative analysis of groups on quantitative characteristics. Correlation analysis using Spearman rank correlation was used to assess the relationship between features. A very significant correlation was observed at r, corresponding to the level of statistical significance $p < 0.01$, a significant correlation — at r, corresponding to the level of statistical significance $p < 0.05$.

Results and discussion

According to spirometry data in the group of patients with mild BA, ventilation disorders of obstructive type were found only in 11 patients (16 %) (Table 1). In quantitative analysis of the FEV_1, mild airway patency disorders (APD) were reported in 3 (4 %) people, moderate APD — in 6 (9 %) patients, severe — in 2 (3 %) people, while the parameters of FVC and VC in all patients were within normal values. We found the decline of MVR_{25-75} in 13 patients (19 %). Similar results were demonstrated in a previous study by Pellegrino R. et al. (2005), which suggests that in the diagnosis of early bronchial obstruction, MVR_{25-75} may be more sensitive than FEV_1 [22].

According to body plethysmography the most pronounced changes were in bronchial resistance during exhalation (Raw_{ex}); this parameter increased in 32 (47 %) subjects, and increase in total bronchial resistance (Raw_t) was also reported in 15 (22 %) subjects and in bronchial resistance during inspiration (Raw_{in}) — in 9 (13 %) people.

In the control group bronchial resistance indices were within normal values in all subjects.

The results of IOM in the group of patients with mild asthma indicated an increase in the resistive component of respiratory impedance at the frequency of the oscillations of 5 Hz Rrs5 in 9 (13 %) patients, deltaXrs5 — in 10 (15 %) patients and an increase in Rrs20 — in 4 (6 %) of the patients. The comparison of the results for indicators in the group allowed to diagnose ventilation disorders of obstructive type, in 14 (21 %) patients, among them in 9 (13 %) patients moderate disorders were revealed and in 3 (4 %) — severe disorders and in 2 (3 %) — extreme disorders. Thus, in 5 (7 %) subjects changes based on IOM were more pronounced in comparison with spirometry.

In the analysis of IOM indicators in the group with mild BA, absolute frequency dependence Rrs5-Rrs20 was the most susceptible to changes, and its increase was found in 48 (71 %) people, of which 42 (61 %) patients had deltaXrs5 and Rrs5 within normal values. These changes were considered as an early sign of peripheral respiratory tract pathology. It is noteworthy that 44 (65 %) people had a larger area above the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX) and the resonance frequency f_{res} shifted to the high frequencies. Quantification of resistive component parameters of respiratory impedance at the frequency of oscillations equal to 5 and 20 Hz, the absolute frequency dependence Rrs5-Rrs20 and deltaXrs5 in patients with mild BA showed the presence of obstructive disorders on the level of the central respiratory tract in 3 patients (4 %), and 1 (2 %) patient was diagnosed with generalized obstruction. In the control group, the values of these indicators did not change.

As a result of the analysis of the relationship between findings of spirometry, body plethysmography and IOM in the group of patients with mild BA, direct and inverse highly significant ($p < 0.001$) correlations were identified.

Therefore, there was a strong positive correlation between bronchial resistance parameter Raw_{ex} and the area above the Xrs curve in the frequency

Table 1. *Parameters of body plethysmography, spirometry and impulse oscillometry in the group of patients with mild asthma and the control group*

Parameters	Mild asthma, n=68		Control, n=41		Significance of differences
	Me[Q1;Q3]		Me[Q1;Q3]		
	n	1	n	2	
VC, %	68	100.9[91.15;109.55]	41	99.1[91.9;107.7]	$\rho_{1-2} = 0.72$
FVC, %	68	99.55[90.2;109]	41	102.8[95;110]	$\rho_{1-2} = 0.43$
FEV_1, %	68	90.75[82.5;98.45]	41	101.5[92.6;109]	$\rho_{1-2} = 0.001$
FEV_1/VC, %	68	77.55[72.25;80.6]	41	88[83;89.6]	$\rho_{1-2} < 0.001$
FEV_1/FVC %	68	77.9[72.17;81.8]	41	86.44[82.08;88.37]	$\rho_{1-2} < 0.001$
MVR_{75-25}, %	68	80.1[75.2;89.35]	41	89.4[82.2;96.8]	$\rho_{1-2} = 0.003$
TLC, %	68	104.6[99.25;110.75]	41	101[95;107.7]	$\rho_{1-2} = 0.057$
RV, %	68	112.05[97.45;137.2]	41	98.1[87.8;110.4]	$\rho_{1-2} = 0.003$
RV/TLC, %	68	106.55[92.05;126.35]	41	94.1[87.1;105.6]	$\rho_{1-2} = 0.013$
FRCρleth, %	68	106.9[88.7;117.2]	41	89.4[83;103.6]	$\rho_{1-2} = 0.001$
Raw_t, kPa•s/l	68	0.21[0.15;0.29]	41	0.16[0.12;0.2]	$\rho_{1-2} < 0.001$
Raw_{ex}, kPa•s/l	68	0.23[0.18;0.35]	41	0.2[0.15;0.24]	$\rho_{1-2} = 0.002$
Raw_{in}, kPa•s/l	68	0.18[0.14;0.26]	41	0.19[0.14;0.22]	$\rho_{1-2} = 0.438$
Zrs5, %	68	127.2[108;138.7]	41	106.4[97.2;122.3]	$\rho_{1-2} < 0.001$
Rrs5, %	68	128.7[95.2;145.2]	41	102[87.1;112]	$\rho_{1-2} < 0.001$
Rrs20, %	68	92.2[73.05;117.55]	41	94.5[73.3;99]	$\rho_{1-2} = 0.247$
(Rrs5-Rrs20)/Rrs5, %	68	20.3[11.4;28.1]	41	12.2[8.6;15.9]	$\rho_{1-2} < 0.001$
(Rrs5-Rrs20)/Rrs20, %	68	25.4[13.0;39.1]	41	13.9[9.4;19.0]	$\rho_{1-2} < 0.001$
Rrs5-Rrs20, kPa•s/l	68	0.09[0.07;0.14]	41	0.04[0.03;0.06]	$\rho_{1-2} < 0.001$
deltaXrs5, kPa•s/l	68	0.1[0.08;0.14]	41	0.09[0.07;0.12]	$\rho_{1-2} = 0.038$
AX, kPa/l	68	0.37[0.2;0.56]	41	0.18[0.15;0.21]	$\rho_{1-2} < 0.001$
DXrs5, kPa•s/l	68	0.07[0.035;0.125]	41	0.04[0.02;0.05]	$\rho_{1-2} < 0.001$
Co5	68	0.78[0.67;0.88]	41	0.72[0.67;0.79]	$\rho_{1-2} = 0.046$
fres, Hz	68	16.5[12.5;19]	41	9[7;11]	$\rho_{1-2} < 0.001$

Note: The significance of differences between groups is calculated using the Mann-Whitney test; differences are significant at ρ <0.05; n is the number of observations

range from 5 Hz to f_{res}, (AX) (r = 0.73, ρ <0.001). Also mean, direct, correlation for Raw_{in}, Raw_t and AX (r = 0.67, ρ <0,001, r = 0.68, ρ <0.001, respectively), mean direct, highly significant correlation of these parameters with the resonant frequency f_{res} (r = 0.53, ρ <0.001, r = 0.54, ρ <0.001, respectively) were found (Fig. 1). Thus, in most patients with clinical manifestations of bronchial obstruction and increased bronchial resistance, there was an increase in the area above the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX).

We also found a mean direct correlation of the Rrs5 parameter with bronchial resistance indicators Raw_{ex} (r = 0.67, ρ <0.001), Raw_{in} (r = 0.66, ρ <0.001), Raw_t (r = 0.67, ρ <0.001) and between Rrs20 and Raw_{ex} (r = 0.54, ρ <0.001), Raw_{in} (r = 0.53, ρ <0.001), Raw_t (r = 0.52, ρ <0.001) (Fig. 2).

Correlation analysis of spirometry and IOM indicators revealed mean inverse correlation between MVR_{25-75} and the following indicators: Rrs5 (r = –0.56, ρ <0.001), AX (r = –0.59, ρ <0.001), absolute frequency dependence Rrs5-Rrs20 (r = –0.50, ρ <0.001) and resonance frequency f_{res} (r = –0.66, ρ <0.001). Moderate inverse correlation between the Rrs20 indicator and Tiffeneau index (r = –0.50, ρ <0.001), Gensler index (r = –0.54, ρ <0.001), and

moderate inverse correlation between the absolute frequency dependence Rrs5-Rrs20 and FEV_1 (r = –0.46, ρ <0.001), Tiffeneau index (r = –0.49, ρ <0.001), Gensler index (r = –0.45, ρ <0.001) (Fig. 3) were found.

The results obtained suggest that the IOM parameters, such as the area above the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX), the absolute frequency dependence Rrs5-Rrs20 and the resistive component of the respiratory impedance at the oscillation frequency of 5 along with the parameters of spirometry MVR_{25-75}, FEV_1, FEV_1/VC, FEV_1/FVC can indicate the presence of airway patency impairment.

In addition, in the group of patients with mild BA, moderate inverse correlation was established between the VC and FVC parameters and Rrs5 (r = –0.34, ρ = 0.005, r = –0.35, ρ = 0.003, respectively), the absolute frequency dependence Rrs5-Rrs20 (r = –0.31, ρ = 0.011, r = –0.36, ρ = 0.002, respectively), AX (r = –0.32, ρ = 0.009, r = –0.34, ρ = 0.005, respectively) and the resonance frequency f_{res} (r = –0.38, ρ = 0.002, r = –0.43, ρ <0.001, respectively) (Fig. 4).

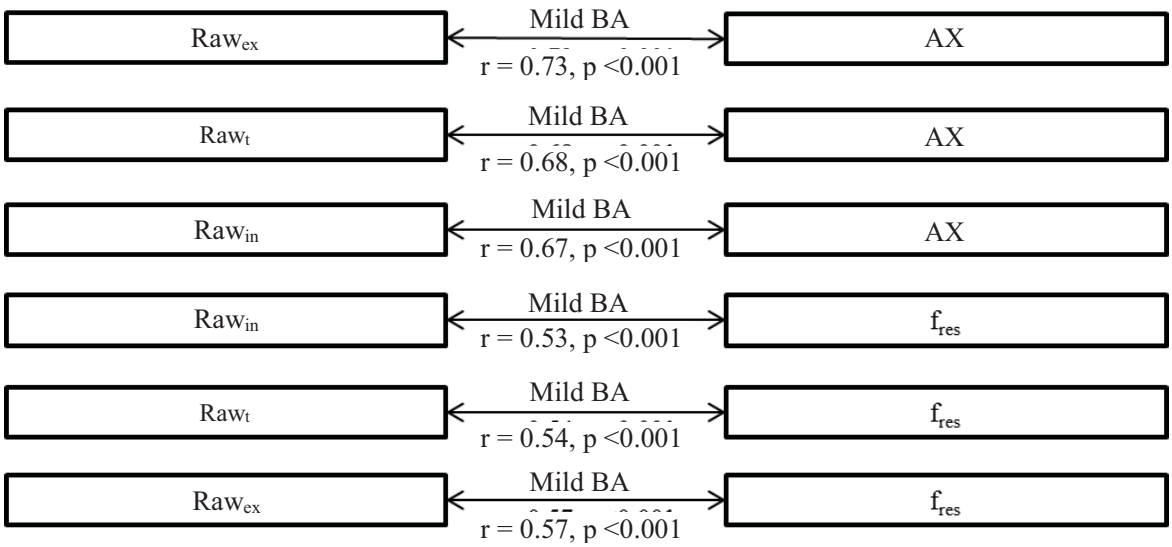

Figure 1. *Correlation of bronchial resistance and IOM parameters in the group of patients with mild asthma*

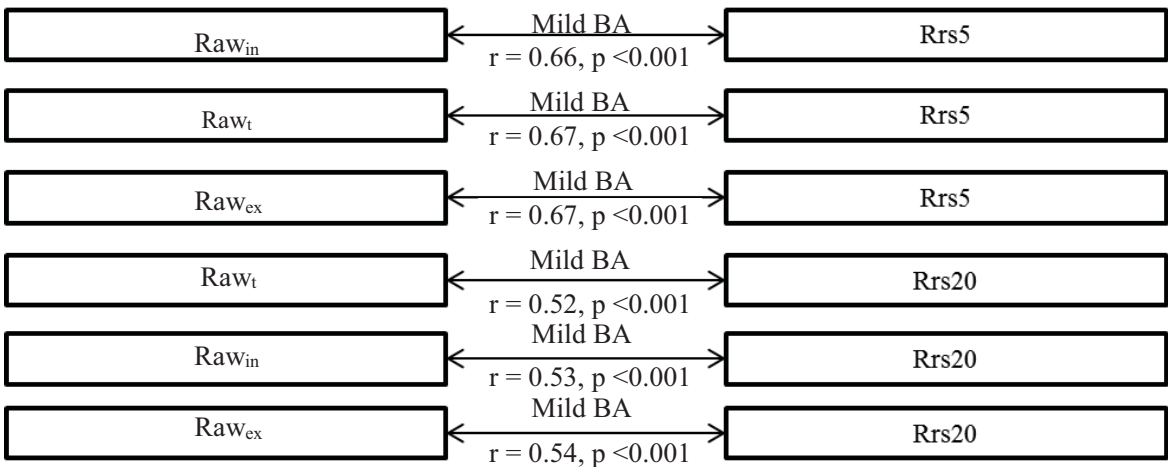

Figure 2. *Correlation of bronchial resistance and the resistive component of the respiratory impedance at the oscillation frequency of 5 and 20 Hz in the group of patients with mild asthma*

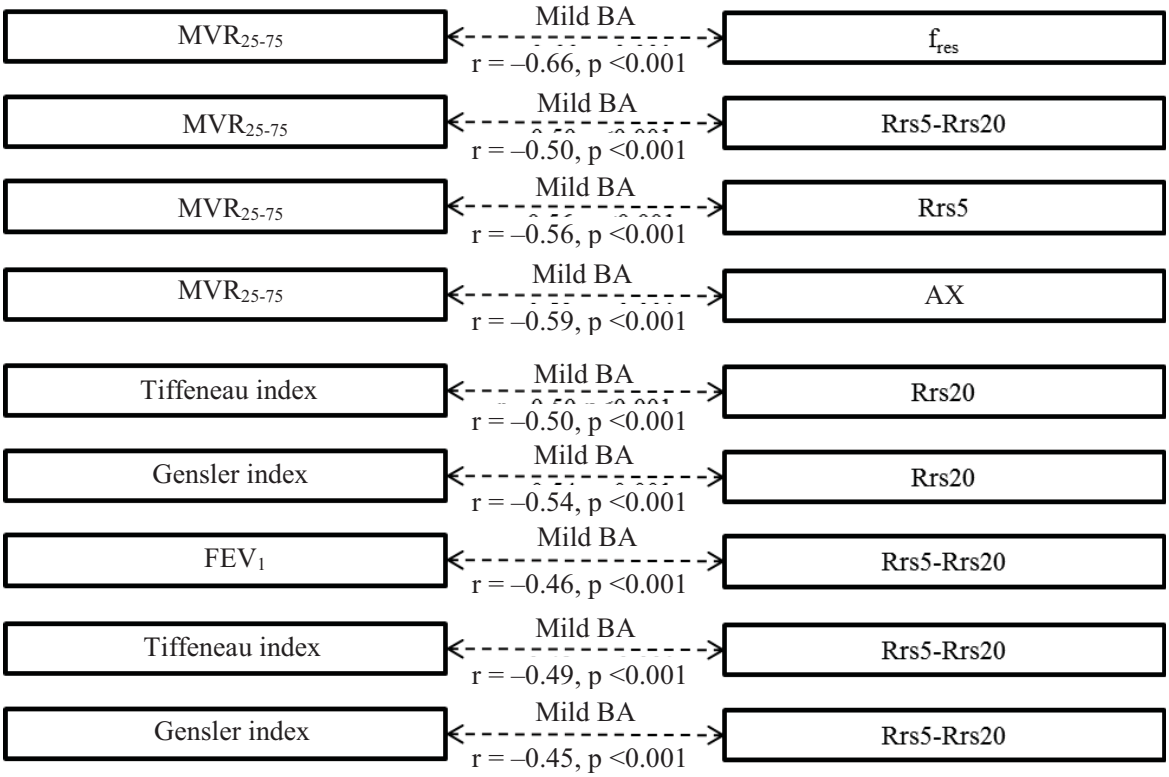

Figure 3. *Correlation of respiration mechanics parameters (MVR_{25-75}, Tiffeneau index, Gensler index, FEV_1) with IOM parameters, resistive component of the respiratory impedance at the oscillation frequency of 5 and 20 Hz, absolute frequency dependence, resonance frequency f_{res} and AX in the group of patients with mild asthma*

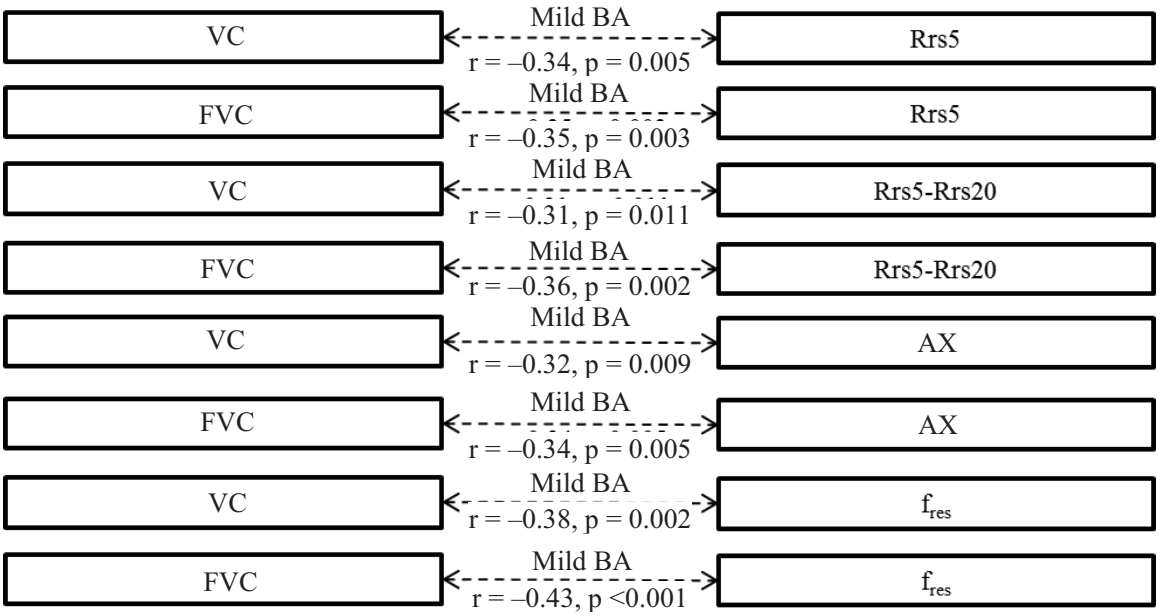

Figure 4. *Correlation of lung volumes (VC, FVC) and the resistive component of the respiratory impedance at the oscillation frequency of 5 and 20 Hz, absolute frequency dependence Rrs, resonance frequency f_{res} and AX in the group of patients with mild asthma*

Thus, the results of the analysis showed that in patients with ventilation disorders of obstructive type, bronchial resistance indicators are significantly correlated with all the main parameters of IOM. The most informative indicators of IOM were absolute frequency dependence Rrs5-Rrs20 and the area above the curve Xrs in the frequency range from 5 Hz to f_{res}, (AX); these indicators were closely correlated with the magnitude of bronchial resistance, and in inverse proportion to rate indicators, such as FEV_1, MVR_{25-75}, FEV_1/VC, FEV_1/FVC. Similar correlations were observed between the VC, FVC and resistive component of the respiratory impedance at the oscillation frequency of 5, 20 Hz Rrs5, Rrs20. Therefore, the lower the rate and the greater the capacity, the greater the absolute frequency dependence Rrs5-Rrs20, AX and Rrs5, Rrs20.

In the future, it is planned to conduct a study with the expansion of the groups of subjects and a more in-depth analysis of the relationship between the indicators of functional tests, including IOM with the severity of obstructive disorders in patients with bronchial asthma.

Conclusion

According to the results of the study, the following conclusions can be made:

1. IOM parameters are significantly correlated with body plethysmography and spirometry parameters, to a greater extent with indicators of bronchial resistance
2. The absolute frequency dependence Rrs5-Rrs20 and the area above the Xrs curve in the frequency range from 5 Hz to f_{res}, (AX) are the most informative parameters of the IOM and are in a closer correlation with the respiratory mechanics parameters
3. Indicators of the resistive component of the respiratory impedance at the oscillation frequency of 5 Hz, 20 Hz, Rrs5, Rrs20 and deltaXrs5 allow to differentiate the localization of the pathological process in the central and peripheral RT and, possibly, in some cases, can be more informative than basic parameters of spirometry; in 5 subjects (7 %), according to IOM, changes were more pronounced in comparison with spirometry.

Conflict of interests

The authors declare no conflict of interests.

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COMPARISON OF THE PREVALENCE AND DYNAMICS OF ANXIETY, DEPRESSION AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC RHEUMATIC HEART DISEASE

Abstract

The objective: The assessment of the severity, prevalence and five-year dynamics of anxiety and depression in those studied with rheumatic heart disease. **Materials and methods.** The study included 168 patients with rheumatic heart disease: mean age 58.69±0.47 years; 141 women (83.93 %) and 27 men (16.07 %). To assess anxiety and depression, the following scales were used: HADS (Hospital Anxiety and Depression Scale), CES-D (Depression Scale of the Epidemiological Research Center), and STAI (State-Trait Anxiety Inventory). Quality of life was assessed using total scales SF-36 (Short Form Medical Outcomes Study), KCCQ (Kansas City Cardiomyopathy Questionnaire), and MHFLQ (Minnesota Living with Heart Failure Questionnaire). **Results.** Initially, patients with rheumatic heart disease had mild depression and anxiety, except for the high level of state anxiety according to STAI — 48.00±0.95. More pronounced depressive disorders were revealed in patients with CHF NYHA III and IV. According to CES-D — 17.58±1.27 for FC I and 23.4±0.75 for FC IV, for HADS — 7.00±0.64 for FC I and 13.6±0.78 for FC IV. Anxiety disorders, on the contrary, were less in III and IV FC CHF: 8.5±0.49 with FC I and 8.2±1.02 with FC IV in HADS. According to STAI state anxiety — 47.58±1.22 (FC I) and 42.8±1.76 (FC IV), for trait anxiety — 42.67±1.08 (FC I) and 40.4±1.85 (FC IV). For the five-year period there was no negative and positive dynamics according to the questionnaires of anxiety and depression. The only exception was the increase in anxiety according to HADS by 0.66 points. In terms of quality of life, there was a decrease in physical health according to SF-36 by 1.78, and in overall summary score according to KCCQ by 1.55 and MHFLQ by –3.99. **Conclusions.** In patients with rheumatic heart disease, the severity of anxiety and depression is insignificant and does not increase during five years of observation. Indicators of depression are more pronounced in the group with CHF NYHA III and IV, and anxiety indicators in patients with CHF NYHA I and II. An increase in depression rates in subjects with rheumatic heart disease is associated with a deterioration in the quality of life. With an improvement in the quality of life parameters, depressive symptoms decrease, and anxiety rates increase.

Key word: *rheumatic heart disease, anxiety, depression, quality of life*

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CES-D — depression scale of Center for Epidemiological Studies, EQ-5D — EuroQol Group, HADS — Hospital Anxiety and Depression Scale, KCCQ — Kansas City Cardiomyopathy Questionnaire, MHFLQ — Minnesota Living With Heart Failure Questionnaire, SF-36 — Short Form Medical Outcomes Study, STAI — State-Trait Anxiety Inventory, VAS — visual analog scale, CAD — coronary artery disease, TA — trait anxiety, SA — state anxiety, FC — functional class, AF — atrial fibrillation, CRHD— chronic rheumatic heart disease, CHF — chronic heart failure

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The high prevalence of anxiety and depressive disorders and their relationship with cardiovascular diseases has long been known. Anxiety and depression significantly affect patients' quality of life, their adherence to treatment and performance [1]. It is noted that people with depression often develop coronary artery disease, myocardial infarction, stroke and sudden death, even in the case of unexpressed depressive symptoms [2]. In addition, both the cardiovascular diseases themselves lead to anxiety and depressive disorders, and anxiety with depression affect heart rhythm disturbances, the duration of angina attacks and the frequency of coronary events. At the same time, anxiety disorders are associated with an increase in the risk of coronary artery disease (CAD) by 26–41 %, and cardiovascular disease by 52 % in the case of long-term follow-up [3, 4]. Literature indicates that the increase in the severity of depression by 1 point on the Zung self-assessment scale increases mortality by 8 % [5]. But data on the relationship between anxiety disorders and increased risk of mortality from coronary artery disease has not been obtained [3]. However, anxiety disorders may be associated with an increased risk of coronary events [6].

The outcome of most cardiovascular diseases is chronic heart failure (CHF), which largely determines their course and prognosis. The prevalence of anxiety and depressive disorders in patients with CHF of ischemic etiology ranges from 14 % to 60 % according to the literature. Severe depression is seen in 17.25 % of the subjects, moderate — in 20.9 % and mild — in 27.3 % [7]. According to the literature, the severity and frequency of anxiety and depressive disorders in CHF can be influenced by the following factors [8–12]: functional class (FC) of CHF (especially III and IV FC); its duration; the age of the patient (older or younger than 60 years); sex (in case of ejection fraction less than 40 % females dominate); concomitant pathology (diabetes mellitus); economic status (socially vulnerable patients and unemployed); level of education (lower level of education); place of residence (living in the city); degree of awareness on CHF (lack of information about CHF and methods of its treatment).

Depression is an additional factor affecting the physical, mental and social activity of patients with CHF. Often accompanying CHF paroxysmal and permanent atrial fibrillation leads to increased anxiety and depression [1]. Depressive disorders also affect the life expectancy of patients with CHF. It is believed that the mortality of patients with depression is 25 % compared to 11.3 % of patients without signs of disorders. Data on the dynamic monitoring of patients with CHF due to acquired heart defects [13] and the incidence of anxiety and depression in such patients are few [14].

The **objective** of the work was to assess the severity, prevalence and five-year history of anxiety and depression in subjects with chronic rheumatic heart disease (CRHD).

Materials and methods

The study included 168 patients with CRHD who underwent inpatient treatment at the regional cardiology dispensary and signed an informed consent. The average age of the subjects was 58.69±0.47 years; 141 women (83.93 %) and 27 men (16.07 %). From subjects diagnosed with CRHD we selected only patients who had mitral stenosis as a reliable symptom of rheumatic defect. The absence of mitral stenosis was the exclusion criterion.

To obtain more objective estimates of FC we used a 6-minute walk test. Twenty-two subjects (13.1 %) had FC I, 77 (45.8 %) — FC II, 60 (35.7 %) — FC III, 9 (5.4 %) — FC IV. In addition, dyspnea was assessed on a visual analog scale (VAS) of 100 mm. Echocardiography was carried out on Philips Affinity 50 with the assessment of the linear dimensions of the heart, the pressure gradients on the valves.

The following scales of anxiety and depression assessment were used in the assessment of anxiety and depression: hospital anxiety and depression scale (HADS) with assessment: 0–7 — normal; 8–10 points — subclinically expressed anxiety/depression; 11 points and more — clinically expressed anxiety/depression. Depression Scale of the Center for Epidemiological Studies (CES-D) with assessment: 0–17 points — normal; 18–26 points — mild depression; 27–30 points — moderate depression; 31 points and above — severe depression. State-Trait Anxiety Inventory (STAI) with assessment of anxiety: up to 30 points — low, 31–44 points — moderate; 45 and more — high [15]

with the assessment of state (SA) and trait anxiety (TA). TA reflects a person's predisposition to anxiety and suggests a tendency to perceive many situations as threatening. TA is activated by the perception of certain stimuli, which are regarded as dangerous for self-assessment and self-esteem. SA (or situational anxiety) is characterized by subjectively experienced emotions: tension, anxiety, nervousness and restlessness. SA occurs as an emotional reaction to a stressful situation and can be different in intensity and responsiveness over time.

Quality of life was assessed using the general questionnaire titled Short Form Medical Outcomes Study (SF-36 V. 1) evaluating the quality of life for the last 4 weeks with scores on 8 scales and forming two summary measures: physical and mental health component. Kansas City Cardiomyopathy Questionnaire (KCCQ) with an assessment of two total indicators: functional status and total clinical indicator. Specific for CHF Minnesota Living With Heart Failure Questionnaire (MHFLQ), consisting of 21 points. The scale of life quality assessment from the EuroQol Group EQ-5D questionnaire was also used.

The IBM SPSS Statistics 23.0 software with t-test evaluation for independent samples, Kruskal-Wallis test and Pearson correlation was used for statistical processing of the obtained data. The differences were considered as statistically significant at $p < 0.05$.

Results

Initially, the prevalence of CES-D depression in subjects with CRHD was: 39.9 % — normal; 38.7 % — mild depression; 8.9 % — moderate depression; and 12.5 % severe depression. By HADS (depression): 39.9 % — normal; 36.3 % — subclinically expressed depression; 23.8 % — clinically significant depression. Incidence of anxiety by HADS (depression) was: 36.9 % — normal; 32.2 % — subclinically expressed anxiety; 30.9 % — clinically significant anxiety. According to STAI, mild SA occurred in 3.0 % of the subjects; moderate SA — in 33.3 % of the subjects; severe SA — 63.7 % of the subjects. The prevalence of TA in STAI was low in 10.7 %; moderate in 52.4 %; high in 36.9 % of patients with CRHD. The average distance in 6-minute walk test in patients was 330.91±8.42 meters and for 5 years it slightly decreased to 324.92±8.42 meters, but the value remained within the range of CHF of FC II. Dyspnea, which is one of the main symptoms of CHF, although it increased according to VAS for dyspnea assessment from 47.21±2.90 mm to 50.58±3.74 mm, the increase was insignificant.

When assessing the echocardiographic parameters (Tab. 1) there was a statistically significant increase in the size of the left atrium by 0.25 cm, the aorta — by 0.12 cm and a decrease in mitral valve orifice area — by 0.10 cm^2 for five years. Pressure on the aortic valve also increased in patients with combined

Table 1. *5-year dynamics of echocardiographic parameters*

Echocardiographic parameters	Average value		p
	Initial	After 5 years	
Aorta, cm	3.27±0.03	3.39±0.03	0.001
Left atrium, cm	4.83±0.06	5.08±0.06	0.001
LVED, cm	5.51±0.06	5.51±0.06	0.951
LVES, cm	3.64±0.05	3.63±0.06	0.771
Ejection fraction, %	61.97±0.5	61.38±0.7	0.362
IVS, cm	1.16±0.03	1.14±0.03	0.550
LVPW, cm	1.11±0.03	1.29±0.32	0.139
Right ventricle, cm	2.83±0.05	2.74±0.06	0.127
Right atrium, cm	4.62±0.27	4.80±0.16	0.585
MVA, cm^2	1.88±0.05	1.78±0.04	0.026
Left ventricle — aorta pressure, mmHg	25.51±2.00	32.98±3.74	0.006
Pressure in TV, mmHg	33.89±1.02	35.16±1.36	0.348

Note: LVED — left ventricle end-diastolic dimension, LVES — left ventricle end-systolic dimension, IVS — interventricular septum, LVPW — left ventricular posterior wall, MVA — mitral valve area, TV — tricuspid valve

aortic stenosis by 7.47 mmHg. There were no significant changes in other indicators over the time.

Evaluation of the total indicators of changes in quality of life over time showed the following results (Tab. 2). In subjects, changes in indicators of the physical health component SF-36 by 1.78, functional status according to KCCQ — by 1.55 and MHFLQ — 3.99 over the 5 years were statistically significant, which reflected deterioration of quality of life. For other values, there was also a deterioration in the quality of life by 0.78 in the mental health component of SF-36 and by 2.31 on EQ-5D scale, also an improvement by 1.76 on the KCCQ clinical status scale, but the changes were statistically insignificant.

With the above-mentioned changes in the test distance of 6-minute walk, dyspnea, echocardiographic parameters and quality of life, the subjects had mild depression according to CES-D both at baseline (20.02±0.86) and after 5 years of follow-up (20.63±0.79). According to the HADS questionnaire, although the indicators of depression conditionally increased from normal values (7.98±0.35) to subclinically expressed depression (8.04±0.36), the growth was statistically insignificant (Tab. 3). The rate of anxiety according to HADS matched subclinically expressed anxiety — 8.06±0.39 and slightly, but statistically significantly increased after 5 years (8.72±0,32). The results of the evaluation for STAI questionnaire showed a high level of SA equal to 48.00±0.95 and 46.9±1.04 (after 5 years) and moderate level of TA equal to 39.58±0.86 and 39.66±0.89 (after 5 years) without statistically significant changes in indicators.

When the dependence of anxiety and depressive disorders on CHF was initially assessed, it was found that the depression index according to CES-D increased by 5.8 points from 17.6±1.27 in the group with FC I to 23.4±0.75 in the group with FC IV, but the increase was insignificant (Tab. 4).

Table 2. *5-year quality of life dynamics*

Quality of life questionnaires	Average value		p
	Initial	After 5 years	
Scale EQ-5D	52.86±1.70	50.55±1.96	0.233
SF36, Physical health	35.79±0.78	34.01±0.77	0.008
SF36, Mental health	38.94±1.13	38.16±0.88	0.505
KCCQ, Overall summary score	22.61±0.78	21.06±0.78	0.020
KCCQ, Clinical summary score	48.70±1.96	50.46±1.72	0.369
MHFLQ	43.79±1.65	47.78±1.96	0.033

Table 3. *Dynamics of anxiety and depression according to the questionnaires*

Scale of anxiety/depression	Mean difference	95 % CI	p
CES-D	–0.61	–1.91 — 0.69	0.357
HADS (anxiety)	–0.66	–1.25 — –0.07	0.280
HADS (depression)	–0.06	–0.71 — 0.59	0.855
STAI (state anxiety)	1.10	–0.41 — 2.61	0.153
STAI (trait anxiety)	–0.08	–1.34 — 1.18	0.900

Note: CI — confidence interval

Table 4. *Changes in anxiety and depression depending on CHF NYHA FC*

Scale of anxiety/depression	p	FC I	FC II	FC III	FC IV
CES-D	0.410	17.6±1.27	20.8±0.85	20.1±0.94	23.4±0.75
HADS (depression)	0.001	7.0±0.64	7.8±0.32	7.9±0.37	13.6±0.78
HADS (anxiety)	0.074	8.5±0.49	8.7±0.41	8.1±0.42	8.2±1.02
STAI (state anxiety)	0.042	47.6±1.22	47.1±0.93	48.4±0.98	42.8±1.76
STAI (trait anxiety)	0.008	42.7±1.08	38.7±0.87	42.0±0.91	40.4±1.85

According to the HADS scale, depression increased from the absence in FC I (7.00±0.64) to clinically significant depression in FC IV (13.6±0.78). Indicators of anxiety, on the contrary, in contrast to the indicators of depression, decreased with the increase of CHF FC. And if the decrease by 0.3 points according to the HADS anxiety scale was insignificant and remained within the range of subclinically expressed anxiety, the decrease in the anxiety indicators of the STAI questionnaire from FC I to FC IV was statistically significant in terms of SA and TA. TA decreased by 2.27 points in moderate anxiety and SA decreased from high anxiety to moderate by 4.78 points.

Re-assessment of anxiety and depressive disorders after five years of follow-up (Tab. 5) although it showed a decrease in depression from the group of FC I to the group of FC IV according to CES-D by 4.58 points, on HADS scale — by 0.58 points, the indicators were not statistically significant. No statistically significant results of increased anxiety on STAI scales were also obtained from the anxiety values: SA by 6.6 points and TA by 2.2 points.

Since the influence of atrial fibrillation (AF) on the course of CHF and quality of life is often discussed in the literature, the indicators of anxiety and depressive disorders were compared depending on the presence of sinus rhythm (49.4 % of the subjects) or permanent AF (51.6 %) (Tab. 6). There were no significant differences in depressive and anxiety disorders between the groups. Depression and CES-D scores were consistent with mild depression, and the HADS score was subclinically expressed depression in both groups. On the HADS scale, there was also subclinically expressed anxiety in both groups. According to the STAI questionnaire, moderate anxiety for TA and high anxiety for SA was revealed both in the case of sinus rhythm and in the case of permanent AF.

Table 5. *Indicators of anxiety and depression depending on CHF NYHA FC after 5 years of observation*

Scale of anxiety/depression	p	FC I	FC II	FC III	FC IV
CES-D	0.539	19.3±2.1	21.0±1.16	19.6±1.18	14.7±1.11
HADS (depression)	0.098	7.3±0.97	8.4±0.43	6.4±0.0.70	6.7±1.48
HADS (anxiety)	0.149	7.9±0.85	8.5±0.49	8.9±0.38	7.0±0.37
STAI (state anxiety)	0.801	48.1±3.07	47.0±1.43	48.3±1.91	54.7±4.82
STAI (trait anxiety)	0.670	39.5±3.13	40.6±1.25	40.0±0.98	41.7±0.84

Table 6. *Severity of anxiety and depression depending on the presence of AF*

Scale of anxiety/depression	p	AF	95 % CI	SR	95 % CI
CES-D	0.883	19.3±0.59	18.34–20.47	20.98±0.85	19.31–22.66
HADS (depression)	0.462	7.88±0.33	7.23–8.53	7.95±0.31	7.34–8.57
HADS (anxiety)	0.945	7.72±0.34	7.04–8.40	9.02±0.34	8.34–9.69
STAI (state anxiety)	0.214	47.8±0.80	46.22–49.38	47.42±0.83	45.79–49.06
STAI (trait anxiety)	0.287	41.28±0.73	39.82–42.74	40.81±0.78	39.27–42.35

Note: AF — atrial fibrillation, SR — sinus rhythm, CI — confidence interval

Table 7. *Correlation of total scales of quality of life questionnaires with anxiety and depression indicators*

Scale of anxiety/depression	SF 36 (PH)	SF 36 (MH)	KCCQ (OSS)	KCCQ (CSS)	MHFLQ	Scale EQ-5D
CES-D	–0.44**	–0.67**	–0.37**	–0.51**	0.52**	–0.32**
HADS (depression)	–0.46**	–0.64**	–0.41**	–0.38**	0.46**	–0.39**
HADS (anxiety)	–0.32**	0.42*	–0.23**	–0.45**	0.47**	–0.11
STAI (state anxiety)	0.437**	0.58**	0.37**	0.52**	–0.59**	0.28**
STAI (trait anxiety)	0.30**	0.47**	0.26**	0.44**	–0.51**	0.21**

Note: PH — physical health, MH — mental health, OSS — overall summary score, CSS — clinical summary score,
* — correlation is significant at the level 0.05, ** — correlation is significant at the level 0.01

The correlation analysis revealed the inverse relationship of average strength between depression indicators on the CES-D scale and quality of life: mental health component of SF-36, total clinical indicator of KCCQ and MHFLQ (Tab. 7). And a direct relationship of average strength between the values of reactive anxiety by STAI with the mental health component of SF-36 and the total clinical indicator of KCCQ. Overall, using all the main scales of the questionnaire of quality of life, there was a significant correlation with weak or moderate strength of relation. Anxiety and depressive changes were correlated with the total parameters of SF-36 questionnaire — physical and mental health component; KCCQ — functional status and total clinical indicator and MHFLQ data. The higher the quality of life according to the summary scales of questionnaires, including the EQ-5D scale of health, the greater the severity of anxiety disorders was. And the severity of depression increased as the quality of life decreased.

Discussion

Initially, patients with CRHD had a slight expression of depression and anxiety. The exception was the indicator of SA according to STAI, which had more than 45 points (48.00±0.95) and was consistent with the high level of anxiety. Although in the literature [15] for CHF of non-ischemic etiology, the level of SA is indicated at the level of 34.3±12.5, and TA — 34.5±11.7, and the prevalence of anxiety according to HADS ranges from 24.7 % (moderate) to 32.6 % (high) [8]. During the five-year follow-up period of the study with CRHD there were no negative changes in terms of the 6-minute walk test and VAS for dyspnea. The mitral valve orifice area of 0.1 cm^2 decreased significantly, the linear dimensions of the left atrium increased by 0.25 cm and the quality of life in the physical health component of SF-36 deteriorated by 1.78, the functional status of KCCQ — by 1.55 and MHFLQ — by –3.99. Against this background, for 5 years there were no expressed negative and positive changes according to the questionnaires for anxiety and depression assessment. The only exception was the increase in anxiety according to HADS by 0.66 points.

Changes in the indicators of anxiety and depression were obtained in the initial assessment of patients depending on FC of CHF. The severity of depressive disorders increased in subjects with III and IV FC of CHF. According to CES-D from 17.58±1.27 with FC I to 23.4±0.75 with FC IV, and according to HADS from 7.00±0.64 with FC I to 13.6±0.78 with FC IV, which is consistent with the literature data [8]. On the contrary, anxiety disorders decreased with FC III and IV: from 8.5±0.49 with FC I to 8.2±1.02 with FC IV according to HADS scale. According to STAI questionnaire there was also a reduction of anxiety indicators: according to SA from 47.58±1.22 (FC I) to 42.8±1.76 (FC IV), TA from 42.67±1.08 (FC I) to 40.4±1.85 (FC IV). After 5 years, the reverse pattern was observed: there was a decrease in depression on the CES-D and HADS in subjects with CHF NYHA III and IV and an increase of anxiety indicators on the HADS and STAI in comparison with patients with FC I and II; however, there was no statistical significance of the differences. However, the literature indicates that the level of depression should increase with longer duration of CHF [8].

As it turned out, the presence of permanent AF in subjects with CRHD does not make an additional contribution to the worsening of anxiety and depressive disorders. Anxiety and depression indicators were mostly moderate in the group with AF and sinus rhythm, and did not differ significantly. The literature, on the contrary, indicates an increase in the level of anxiety by 18.2 % and depression by 20.9 % in comparison with patients without arrhythmia [1]. However, this pertains to patients with CHF of ischemic origin.

Since, on the one hand, the presence of anxiety and depression worsens the quality of life of people [11], and on the other hand, the presence of anxiety and depression in itself is a manifestation and outcome of a reduced quality of life, the correlation of these indicators was assessed. Almost all the total scales of non-specific quality of life questionnaires showed an inverse significant correlation at the level of 0.01 in terms of depression and direct anxiety on the scales for SA and TA assessment of the STAI questionnaire with weak-to-moderate strength of relation. This means that the better the quality of life of patients with CRHD, the more pronounced the anxiety and the less pronounced the depression. Similar results were obtained for the CHF-specific MHFLQ questionnaire: the higher

the MHFLQ indicator (worse quality of life), the more pronounced the depression and the less pronounced the anxiety. This is probably due to the fact that anxiety is an emotional reaction and with a prolonged low quality of life grows into depression, and the latter, according to literature, is closely related to the low quality of life [9]. Conversely, patients with better quality of life are more concerned about their health and have an increased level of anxiety.

Conclusion

Thus, in patients with CRHD the severity of anxiety and depression is insignificant and does not increase within five years of follow-up. Indicators of depression are more pronounced in the group of subjects with FC III and IV of CHF, as well as indicators of anxiety in patients with FC I and II of CHF. The increase in the indicators of depression in subjects with CRHD is associated with a deterioration in the quality of life. With the improvement of the quality of life, depressive manifestations decrease, and anxiety indicators increase.

Conflict of interests

The authors declare no conflict of interests.

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CLINICAL CASE OF TREATMENT OF A PATIENT WITH CHRONIC MYELOID LEUKEMIA WITH A MUTATION *BCR-ABL* Y253H AND COMORBIDITIES

Abstract

The article presents information on the methods of diagnosis and targeted therapy of chronic myeloid leukemia (CML). A clinical case of CML with the development of resistance to therapy with 1st generation tyrosine kinase inhibitors (ITK), the appointment of 2nd generation ITK (dasatinib) with regard to comorbidity, the development of adverse events in the form of fibrosing alveolitis and severe pleurisy, translation of nilotitis in the form of fibrosis of the alveolitis and severe pleurisy is considered, but the lack of effect of treatment. The study of the mutational status revealed a *BCR-ABL* Y253H mutation, which made it possible to individualize the patient's therapy, obtain a large molecular response, and overcome undesirable phenomena. The development of resistance or the loss of response to the treatment of ITK in CML with comorbidity requires the timely identification of mutations in the kinase domain of *BCR-ABL* and contributes to the selection of early personalized therapy for a particular patient.

Key words: *clinical case, chronic myeloid leukemia, tyrosine kinase inhibitors, resistance, BCR-ABL mutation*

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BC — blast crisis, MMR — Major Molecular Response, TKI — tyrosine kinase inhibitors, CHR — Complete Hematologic Response, CCyR — Complete Cytogenetic Response, APh — accelerated phase, CML — chronic myeloid leukemia, CPh — chronic phase

Introduction

Chronic myeloid leukemia (CML) is a chronic disease of blood and bone marrow, a clonal myeloproliferative process that develops as a result of malignant transformation in early hematopoietic progenitor cells [14].

The incidence is approximately 1:100.000 of the population. Peak incidence occurs between the ages of 30–50 years, and about 30 % of the patients are older than 60 years [3, 13].

The unique feature of CML is the presence of a specific marker in tumor cells: t (9;22) (q34;q11) translocation, known as the Philadelphia chromosome (Ph-chromosome) and, respectively, chimeric oncogene *BCR-ABL*. The production of *BCR-ABL*-dependent tyrosine kinase (P210 protein) plays a key role in leukemic cell transformation in CML [1, 3, 9].

Presence of CML can be assumed on the basis of the following clinical and complete blood count data: leukocytosis, myeloid shift, basophilia and

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eosinophilia, anemia, thrombocytosis or thrombocytopenia, hepato-and splenomegaly. Detection of Ph chromosome by cytogenetic method or *BCR-ABL* gene by molecular genetic method is mandatory for diagnosis of CML [14].

Three phases, which reflect the degree of disease progression, are distinguished in the clinical course of CML: chronic phase (CPh), accelerated phase (APh), blast transformation phase or blast crisis (BC). The disease can be newly diagnosed at any stage of the clinical course.

The aim of the modern therapy of CML is the maximal suppression of the Ph-positive tumor clone and the achievement of remission. The modern standard of treatment is therapy with *BCR-ABL* tyrosine kinase inhibitors (TKI). These medicines have a mechanism of targeted effect on *BCR-ABL*-positive tumor cells. This reduces the risk of disease progression and increases patient survival [1, 3, 8, 18]. CML treatment regimens have a clear procedure and are divided into first, second and third lines [2]. The remission of CML is determined by the following concepts: Complete Hematologic Response (CHR) — the number of blood cells is within the normal range and studies do not reveal immature forms of leukocytes. Spleen size is reduced to the normal. Complete Cytogenetic Response (CCyR) — no cells with Philadelphia chromosome (*BCR-ABL*) are revealed by bone marrow cytogenetics. Major Molecular Response (MMR) — PCR test still reveals *BCR-ABL*, however, at a low level (less than 0.1 %). Such response is considered optimal among experts. Complete Molecular Response (CMR) — PCR test still reveals *BCR-ABL*, however, at a very low level up to the technical detection limit (the level is lower than 0.01 % at MR4 and lower than 0.0032 % at MR4.5). Molecularly Undetectable Disease — PCR test does not reveal *BCR-ABL* in the blood or bone marrow [5, 15]. However, most patients may still have a very small number of copies of the *BCR-ABL* gene that are not technically detectable.

Mutational analysis of *BCR-ABL* is carried out in the acceleration phase and in the blast crisis. Also, the presence of the *BCR-ABL* tyrosine kinase domain mutations is recommended to be studied in case of treatment failure and before TKI switching [12, 16, 19]. Mutation in the *BCR-ABL* gene in particular is a common cause of the formation of resistance to TKI therapy, which is found in approximately 16–20 % of patients [4, 6, 7, 21].

A clinical case of a patient with chronic myeloid leukemia, resistance to target therapy with tyrosine kinase preparations and having the *BCR-ABL* mutation Y253H is presented. According to the literature, this mutation occurs in CML in 6–10 % of all cases of the *BCR-ABL* kinase domain mutations and is characterized by the most unfavorable prognosis and short survival, even worse than with the T315I mutation [17].

Case Report

Patient F., 64 years old, was first admitted to the Hematology Department in November 2011 for examination and treatment with the following preliminary diagnosis: Chronic myeloid leukemia, chronic phase. Upon admittance complained of aching pain in the left upper quadrant while in the left side position, fatigue, sweating, fever up to 37 °C, headache. Felt sick for a month. The examination at the local health facilities revealed changes in the complete blood count — leukocytosis, thrombocytosis; ultrasound scanning revealed splenomegaly (+5 cm). To clarify the diagnosis, the patient was referred to a hematologist for consultation. Past medical history includes childhood infections, ARVI, tonsillitis, surgical treatment for purulent process in the coccyx area in 1986. Coronary heart disease, postinfarction (2002) cardiosclerosis. Allergic and family history are not compromised. No bad habits. Physical examination results: state of moderate severity, clear consciousness, active position, skin is pink, clean, moist, subcutaneous tissue of moderate development, body temperature is 37.2 °C. No swelling is detected. Lymph nodes are not palpable. Vesicular breathing over the lungs, no crackles. Respiratory rate is 17 breaths per minute Heart sounds are muffled, regular. BP 145/90 mm Hg, HR — 72 bpm. Digestive organs: tongue is moderately white. Abdomen is soft, moderately painful in the left upper quadrant. Liver is +2 cm from the costal margin, spleen is +4–5 cm from the costal margin. Ultrasound scanning: enlarged spleen, dimensions: 186×76×102 mm, enlarged liver +10 cm, left kidney cyst, diffuse changes of pancreas.

Complete blood count (CBC) reveals leukocytosis, thrombocytosis, leukocyte left shift to poorly differentiated forms of neutrophils: erythrocytes — 4.10×10^{12}/l, hemoglobin — 115 g/l, mean corpuscular volume — 87, platelets — 1277×10^{9}/l, leukocytes — 137×10^{9}/l, blasts — 2 %, promyelocytes — 4 %, myelocytes — 17 %, monocytes — 3 %, lymphocytes — 8 %, segmented neutrophils — 52 %, stab cells — 2 %, immature neutrophils — 2 %, basophils — 10 %. Bone marrow cell differential count: myelocaryocytes — 255,000, megakaryocytes — 210, myeloblasts — 13.0 %, promyelocytes — 1.0 %, myelocytes — 19 %, metamyelocytes — 4 %, stab cells — 12.7 %, segmented neu. — 26.0 %, e — 11 %, l — 1 %, m — 3 %, normoblasts — 9 %. Conclusion: bone marrow is hypercellular, polymorphic. Irritated megakaryocyte lineage. Minor irritation of myeloid lineage. Increased number of blast cells. Increased eosinophil count to eosinophilic myelocytes. Erythroid lineage is narrowed. Specific translocation t (9; 22) (q34; q11), so-called Philadelphia chromosome (Ph-chromosome), was discovered in 100 % of metaphases by cytogenetic study.

Based on clinical, laboratory data and cytogenetic studies, according to WHO and ELN criteria, a clinical diagnosis was established: *Principal:* Chronic myeloid leukemia, chronic phase. *Secondary:* Coronary artery disease. Postinfarction cardiosclerosis (2002). Hypertension stage II, grade 3, risk 4 (according to the Russian Hypertension Classification).

To manage leukocytosis and thrombocytosis the patient received therapy with hydroxycarbamide (Hydrea) at a dose of 2000 mg/day. To prevent complications associated with tumor lysis syndrome in the cytoreduction period, the patient took allopurinol 300 mg/day, combined with copious hydration regimen. From the end of December 2011, the patient started taking 1st line tyrosine kinase inhibitors (TKI) with imatinib (Gleevec) 400 mg/day on an outpatient basis with a positive effect. From June 2012, the deterioration of hematological parameters occurs: leukocytosis — 16.5×10^{9}/l, thrombocytosis — 1863×10^{9}/l. The absence of Hematological and Cytogenetic Response was an indication for increasing the dosage of imatinib (Philachromin) to 600 mg per day.

In July 2012, the deterioration of general well-being, the appearance of severe shortness of breath during exercise developed. An additional examination was carried out, the patient was consulted by a cardiologist, pulmonologist; a diagnosis was established: Interstitial lung disease. Fibrosing alveolitis. Respiratory failure II. Emphysema. Therapy with prednisolone 30 mg per day was prescribed with a gradual decrease of the dose, verospiron 25 mg in the morning constantly. The patient felt satisfactory.

In October 2012, a change in the complete blood count, an increase in platelet level to 3500×10^{9}/l was detected again. Reaferon 3 MIU intramuscularly every other day, hydroxycarbamide (Hydrea) 2000 mg per day were added to the TKI treatment, however, normalization of CBC was not achieved.

In June 2013, the patient was admitted to the Hematology Department due to increasing fatigue, dyspnea, absence of Hematological and Cytogenetic Responses. Leukocytosis, thrombocytosis, left leukocyte shift were still present in CBC: ESR — 39 mm/hour, leukocytes — 39×10^{9}/l, erythrocytes — 3.62×10^{12}/l, hemoglobin — 134 g/l, platelets — 1488×10^{9}/l, blasts — 2 %, promyelocytes — 4 %, myelocytes — 21 %, immature — 5 %, stab — 9 %, segmented — 39 %, eosinophils — 3, monocytes — 55 %, basophils — 18 %, lymphocytes — 8 %, normoblasts — 1:100. As a result of the 1st line therapy failure, the patient was switched to the 2nd line of TKI therapy. When choosing medication, the concomitant diseases of the patient were taken into account: as he suffered myocardial infarction in 2002 and has a high risk of cardiovascular complications, dasatinib therapy (Sprycel) was started at a dosage of 100 mg per day. The therapy was tolerated satisfactorily. During the treatment, Complete Hematological Response was achieved within a month. On 02.10.2013, a molecular genetic study to determine the expression of the *BCR-ABL* gene returned a negative result, which indicates the achievement of Complete Molecular Response.

However, in December 2013 a marked deterioration of health, aggravated dyspnea, cough with mucoid sputum, fever were observed. In January 2014, the patient was again admitted to the Hematology Department in a severe condition. According to the results of the examination, a diagnosis

was established: Bilateral hydrothorax. Respiratory failure II (Fig. 1).

Fluid retention (pleural and pericardial effusions, pulmonary edema) is one of the frequent adverse effects of dasatinib (Sprycel) treatment. In this regard, the patient was switched to nilotinib (Tasigna) 400 mg 2 times a day. The medication was tolerated well, the condition was satisfactory. CBC: ESR — 9 mm/hour, leukocytes — 5.6×10^{9}/l, erythrocytes — 5.0×10^{12}/l, hemoglobin — 138 g/l, platelets — 206×10^{9}/l. Molecular genetic study on

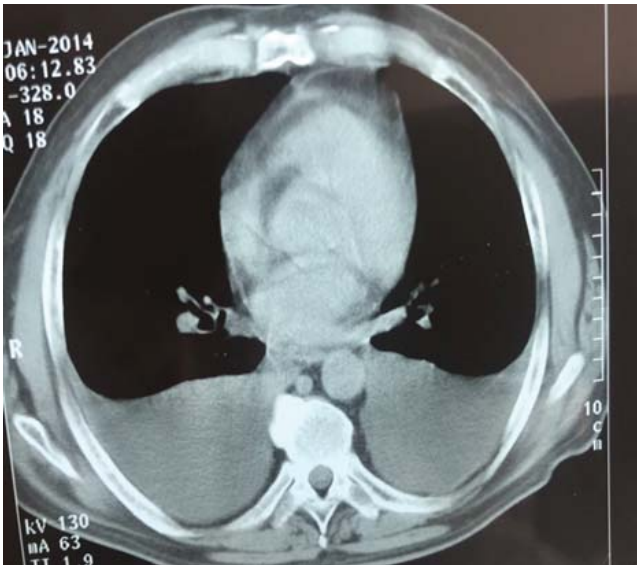

Figure 1. *Bilateral hydrothorax. One of a series of images of a computerized tomography of the chest from January 6, 2014*

22.10.2014 showed that the expression of the *BCR-ABL* gene is 0.13 %. Response to therapy: Complete Hematological Response and Major Molecular Response were achieved.

In August 2015, after suffering moderately severe acute respiratory viral infection, deterioration of blood count was observed. Leukocytosis and thrombocytosis were observed in CBC: leukocytes — 19.0×10^{9}/l, platelets — 1180×10^{9}/l. The treatment was supplemented with Reaferon at a dose of 3 MIU every other day, the effect was insignificant. Cytogenetic study: Ph-chromosome in 100 % of metaphases. Molecular genetic study: expression of the *BCR-ABL* gene — 10.04 %. The therapy was continued.

In November 2016, cytogenetic and molecular studies showed negative changes. A molecular genetic study on 10.11.2016 showed that the expression of the *BCR-ABL* gene was 53.3 %. Due to the failure of therapy, analysis of mutations of the *BCR-ABL* kinase domain was performed, and the Y253H mutation with resistance to imatinib, nilotinib, moderate resistance to dasatinib, sensitivity to bosutinib (Table 1) was detected.

Due to the progressive course of the disease, presence of bosutinib-sensitive mutation, development of pleurisy earlier during dasatinib therapy (Sprycel), the patient was consulted in the FBHI „V.A. Almazov NMRC" of the Ministry of Health of the Russian Federation. Principal Diagnosis:

Table 1. *Dynamics of drug administration and patient treatment results*

Medicine	Period of Therapy	Hematologic Response	Cytogenetic Response	Molecular Response	Adverse Effects, Complications
Imatinib 400 mg/day	From December 2011	PHR	No	No	Edema
Imatinib 600 mg/day + Reaferon	From June 2012	No	No	No	Interstitial pneumonia — July 2012
Dasatinib 100 mg/day	From June 2013	CHR	CHCyR	CMR (2.10.13)	bilateral hydrothorax, Respiratory failure II — December 2013
Nilotinib 400 mg/day	From January 2014	CHR	CHCyR	MMR — 0.13 % (22.10.14)	No
+ Reaferon 3 MIU 3 times/ week	From August 2015	Loss of HR after ARVI	Loss — 100 %	Loss of MR — 10 %, further 53 % (November 2016)	Y253H mutation detected
Dasatinib 100 mg/day	From January 2017 till present	CHR	MCyHR	MMR — May 2017	Dyspnea, cough

Chronic myeloid leukemia, accelerated phase. Cytogenetic resistance and 3rd-4th grade intolerance on the background of therapy with imatinib. Y253H mutation. Secondary: CHD Postinfarction cardiosclerosis (2002). Hypertension stage II, grade 3, risk 4 (according to the Russian Hypertension Classification). Fibrosing alveolitis. Emphysema. Pneumosclerosis. Respiratory failure I, non-acute. Recommended treatment according to vital indications preferably with bosutinib or dasatinib.

From January 2017 till present, the patient receives treatment with dasatinib (Sprycel). The condition is satisfactory. CBC from May 2018: ESR — 17 mm/hour, leukocytes — 4.2×10^9/l hemoglobin — 116 g/l, platelets — 116×10^9/l. Complete Hematological Response, Complete Cytogenetic Response and Major Molecular Response are achieved. There are no serious AEs.

Discussion

The patient was diagnosed with chronic myeloid leukemia based on clinical and laboratory data and cytogenetic study with detection of the pH-chromosome, according to WHO and ELN criteria. Currently, the main way of therapy and standard of treatment is therapy with the inhibitor of *BCR-ABL* tyrosine kinase (TKI) [1, 2]. These medicines have a mechanism of targeted effects on *BCR-ABL*-positive tumor cells and should be prescribed to all newly diagnosed patients [3, 13]. To achieve the goal of modern treatment of CML — the maximum suppression of Ph-positive tumor clone, as the first line of therapy, TKI of the 1st generation imatinib (Gleevec) 400 mg/day was selected. Because of absence of Cytogenetic Response and hematological remission, the dose of imatinib was increased to 600 mg per day. Despite the increase in the dose, no significant effect of treatment was obtained. This was an indication for a shift to the 2nd line TKI therapy. Dasatinib therapy was started (Sprycel) at a dose of 100 mg per day. Complete Hematological and Molecular Response was achieved during the treatment. However, therapy was complicated by the manifestation of non-hematological toxicity of the medicine in the form of fluid accumulation in body cavities with the development of severe pleurisy [4, 11]. The mere fact of the appearance of pleural effusion on the background of dasatinib therapy does not worsen the prognosis, but reduces adherence to the treatment, disrupting the continuity of the therapy. It was decided to change the medication to nilotinib (Tasigna) at a dosage of 400 mg 2 times a day. Response to therapy: Complete Hematological Response, Complete Cytogenetic Response, Major Molecular Response. After acute respiratory viral infection, a deterioration of blood parameters occurred. A loss of Cytogenetic and Molecular Responses was noted. When ascertaining treatment failure, *BCR-ABL* mutation analysis is advisable. [10]. Mutations cause low sensitivity and full resistance to TKI therapy. The patient was found to have the Y253H mutation with resistance to imatinib, nilotinib, moderate resistance to dasatinib, sensitivity to bosutinib. The literature describes mutations that cause low sensitivity of nilotinib therapy: Y253H, E255K/V, F359V/C. When these mutations are detected, dasatinib therapy is preferable [3, 7]. According to S. Severini (2016), the Y253H mutation is more common with relapses of the second line therapy with nilotinib [20].

Considering the presence of the Y253H mutation, concomitant diseases, the clinical course of disease, and the patient's adherence to treatment with dasatinib, regular therapy with II-generation TKI — dasatinib (Sprycel) 100 mg per day was continued. The medication was tolerated satisfactorily, no adverse effects recurred. To assess the condition, monitoring of the treatment and results is carried out. In the course of therapy, Complete Hematological, Cytogenetic and Major Molecular Responses were obtained, which indicates the correct tactics of management of the patient.

Conclusion

The development of resistance or loss of response to TKI treatment in chronic myeloid leukemia with comorbidity requires timely identification of mutations in the *BCR-ABL* kinase domain and contributes to the selection of early personalized therapy for a particular patient.

Conflict of interests

The authors state that this work, its theme, subject, and content do not affect competing interests

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CASE OF SEVERE JUVENILE-ONSET ANKYLOSING SPONDYLITIS IN A PATIENT WITH RECURRENT UVEITIS

Abstract

The objective of the study: To describe a clinical case of severe juvenile-onset ankylosing spondylitis in a patient with persistently recurrent uveitis. **Materials and methods.** Patient I., 43 years old, was constantly monitored since the age of 26 at the Department of Rheumatology of the Saratov Regional Clinical Hospital with ankylosing spondylitis, an early onset of extra-skeletal manifestations in the form of frequently recurring uveitis, and a number of complications. **Results.** Some complications, which caused complete loss of vision in both eyes, occurred during the observation period due to poor treatment adherence. **Conclusion.** The clinical observation presents some features of the disease course, treatment and the development of complications in the patient with ankylosing spondylitis and recurrent uveitis.

Key words: *ankylosing spondylitis, uveitis, extra-skeletal manifestations, complications*

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AS — ankylosing spondylitis, DMARD — disease modifying antirheumatic drugs, GEBD — genetically engineered biological drugs, GC — glucocorticoids, NSAIDs — nonsteroidal anti-inflammatory drugs, SpA — spondyloarthritis, HJ — hip joint, TEP — total endoprosthesis

Introduction

Spondylarthritis (SpA), due to the variety of its extra-skeletal manifestations, constantly requires differential diagnosis with other rheumatic diseases, in particular, with various inflammatory arthritis. Often, patients with SpA need advice from related specialists, most often ophthalmologists, cardiologists. The extra-skeletal manifestations themselves may be additional risk factors for a severe course of the underlying disease, more rapid progression of complications. The joint work of doctors of several specialties can help in the early diagnosis of non-skeletal manifestations, preventing the future development of severe complications, disability of patients, maintaining the quality of life in such patients.

One of the most common non-skeletal manifestations of SpA are uveitis, which accounts for 20 to 40 % of cases [1, 2]. In numerous eye diseases, the proportion of uveitis in patients with rheumatic diseases accounts for 5–12%. At the same time, uveitis is the cause of blindness in 25 % of cases [3]. Uveit onset, according to the literature, takes place at the age of 32–45 years [4-7].

The most common disease characterized by uveitis is ankylosing spondylitis (AS), although this

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extra-skeletal manifestation occurs in all forms of SpA [8]. With respect to the difference in the incidence of uveitis depending on sex, the data are contradictory. There is evidence of the prevalence of uveitis in males (men:women — 1.1:2.5) [9–11], but according to other studies, the incidence of uveitis in women is 40 %, and in men — 15.8 % [12]. An important component in the diagnosis of AS and associated uveitis is the coordinated work of doctors of two specialties — rheumatologists and ophthalmologists [8]. The severe course of AS itself may portend a severe course of uveitis, and uveitis, in turn, may be an independent factor in the severity of the course of the main rheumatic disease, reflecting the variety of complications [8, 13, 14]. At the same time, there are different views on the severity of some non-skeletal manifestations of AS, including the course of uveitis, the prognosis of which is sometimes considered as favorable: attacks, as a rule, are short-term, manageable by local treatment, including instillations and sub-conjunctival injections of corticosteroids [13].

The article presents a clinical case of severe juvenile-onset ankylosing spondylitis in a patient with recurrent uveitis.

Case report

Female patient E., aged 43 years, is monitored at the Regional Clinical Hospital (Saratov) since 2000 (from the age of 26 years).

From history it is known that at the age of twelve (1986) for the first time arthritis of the ankle and wrist joints developed. For juvenile arthritis, glucocorticoids (GC) were prescribed, which were taken occasionally, briefly, without significant effect. Later, the patient periodically experienced pain of inflammatory nature in the joints, and she used non-steroidal anti-inflammatory drugs (NSAIDs) on here own occasionally with a positive effect to manage it.

At the age of 21 (1995) after the childbirth she noted the increase in the severity of peripheral joints arthritis (hands, feet, elbows, knees, ankles) and the appearance of back pain of an inflammatory nature. She was not examined, was not treated regularly and she periodically took NSAIDs.

At the age of 24 years (1998), acute bilateral anterior uveitis was diagnosed for the first time, the characteristic features of which were the acute onset of the disease, pain in the eyes, lacrimation, photophobia, and decreased vision. Laboratory analysis revealed the presence of HLA-B27. In biomicroscopy, moderate or severe pericorneal injection of the eyeball, edema of the cornea endothelium with the deposition of small and medium-sized precipitates of light gray color, and hyperemia of the iris were determined. A feature of the anterior uveitis was the rapid formation of broad persistent posterior synechiae along the pupillary edge, leading to deformation of the pupil (Fig. 1).

The main characteristic feature of HLA-B27 associated uveitis was its recurrent course with frequent exacerbations. Aggravating factors were general overcooling, stress, and an increase in the activity of arthritis. Clinically, the course of uveitis relapse normally did not differ from the first attack of fibrinous plastic iridocyclitis, but acquired a more severe course with the generalization of inflammation in the posterior parts of the eye and the development of complications, which led to a decrease in visual acuity of less than 0.1 (with correction) of the right eye and further complete loss of vision of the left eye, due to the presence of such complications as secondary glaucoma, retinal detachment, and then subatrophy of the eyeball.

Given recurrent uveitis, the presence of peripheral arthritis, increased erythrocyte sedimentation rate, high CRP level and positive HLA-B27, ankylosing spondylitis was suggested for the first time. From that time, for 5 years, the patient was constantly taking NSAIDs, periodically prednisolone 5 mg

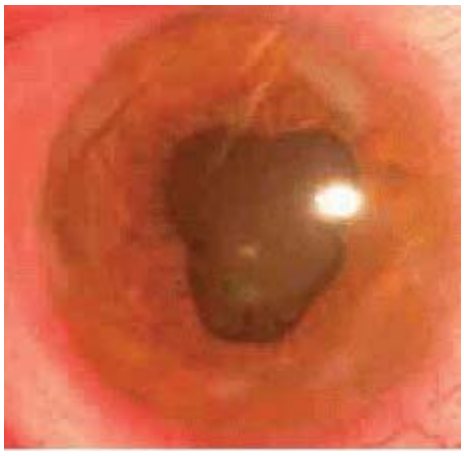

Figure 1. *Pupil deformity. Multiple posterior synechiae*

per day with a slight positive effect in the form of reduced activity of peripheral arthritis. Due to the severity of the disease and frequent relapses of uveitis, the patient was observed and periodically received treatment in the in-patient clinic of eye diseases of Saratov State Medical University n.a. V.I. Razumovsky.

At the age of 26 years (2000) due to the high activity of arthritis of peripheral joints, increased pain in the lumbar spine, increased number of uveitis relapses (up to 4 exacerbations in each eye over the past year), the patient was for the first time hospitalized in the Department of Rheumatology of the Regional Clinical Hospital (Saratov). Examination during hospitalization revealed bilateral sacroiliitis of the stage IV, arthritis of peripheral joints of the stage IV, arthritis of the knee joints of the stage III, ESR 50 mm/h, CRP+++, HLA-B27 positive, BASDAI (the Bath Ankylosing Spondylitis Disease Activity Index) — 7, ASDAS (AS Disease Activity Index) according to CRP — 3.6, and excluded inflammatory bowel disease and psoriasis.

In the hospital, juvenile-onset ankylosing spondylitis of high activity; polyarthritis of the Rg stage IV; bilateral sacroiliitis of the Rg stage IV with systemic manifestations: bilateral recurrent iridocyclitis, acute stage, corneal dystrophy, complicated cataract, vitreous fibrosis, chorioretinal dystrophy, exudative and tractional retinal detachment of both eyes, secondary glaucoma, and subatrophy of the left eye; and secondary bilateral osteoarthritis (gonarthritis) of the Rg stage III were newly diagnosed. Visual functions were light perception with the wrong projection of the light in the right eye and complete blindness of the left eye. NSAIDs with oral and topical GCs (instillations and parabulbar injections in iridocyclitis exacerbation) were prescribed. For secondary glaucoma — locally a combination of ß-blockers and carbonic anhydrase inhibitors. In relation to the development of peripheral arthritis — methotrexate 10 mg per week.

However, after discharge from the hospital, the patient refrained from the recommended therapy, constantly taking only high doses of NSAIDs orally. She did not visit a doctor for a long time. As a result of the lack of adequate therapy, the patient experienced joint deformities: flexural contractures of the wrist joints (Fig. 2), knee, ankle joints, ankylosing and lack of movement in all parts of the spine with BASMI (the Bath Ankylosing Spondylitis Metrology Index) of 0.4 (maximum — 2).

Up to the age of 37 years (2010), the patient was treated on an outpatient basis; attempts were made to prescribe sulfasalazine 500 mg per day. However, on therapy with sulfasalazine, the development of dyspepsia and epigastrial pain were noted, and therefore the drug was withdrawn.

During hospitalization in 2010 at the age of 37 years at the Regional Clinical Hospital, high activity of the disease was detected in the patient (clinically and in the laboratory — ESR 42 mm/h, CRP 61 mg/l). Upon X-ray imaging of the joints, arthritis of the knee joints of the stage IV, aseptic necrosis of the head of the left femur, arthritis of the left hip joint (HJ) of the stage IV and of the right HJ of the stage II were found, and upon X-ray imaging of the spine and pelvis — complete ankylosis, sacroiliitis of the stage IV.

Based on the patient's complaints of low vision in the right eye, no vision in the left eye, the data of medical history (the uveitis in remission), examination data (diffuse cataract, tractional retinal detachment), she was diagnosed with chronic uveitis in remission, dystrophy of cornea, complicated cataract, tractional retinal detachment, chorioretinal dystrophy of the retina of both eyes. Secondary glaucoma, subatrophy of the left eye. Microinvasive vitrectomy with tamponade by perfluoroorganic compounds with replacement with silicone oil, as well as cataract phacoemulsification with implantation of the right eye intraocular lens were performed. In postoperative period: visus OD = counting fingers against the face.

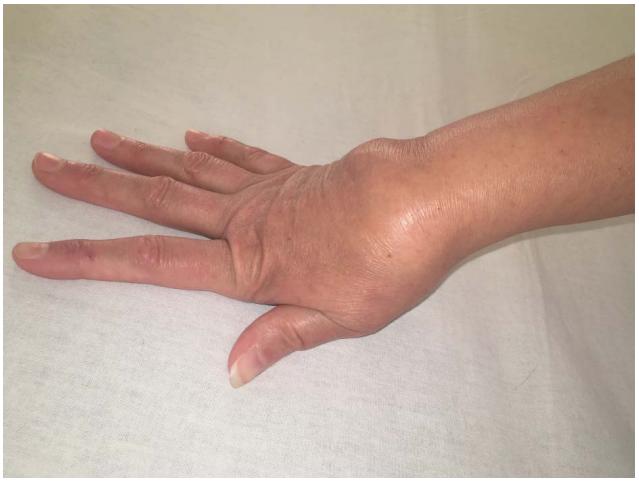

Figure 2. *Deformity of wrist and hand joints*

In the hospital, high doses of GC in the form of pulse therapy with prednisolone 510 mg No. 3 with the clinical effect of reducing the disease activity were administered, and methotrexate therapy at the dose of 15 mg per week was recommended at the outpatient stage. However, the patient again did not take methotrexate, continued taking prednisolone 15–20 mg per week, NSAIDs as required. An orthopedist recommended total endoprosthesis (TEP) of the left hip and knee joints.

Since 2011, due to the increase in AS activity, the patient independently began taking methotrexate 15 mg per week, GC 15 mg per day, NSAIDs daily. TEP of left HJ (Figure 3) was performed in March, 2011, TEP of the left knee joint — in September, 2011, TEP of the right knee joint — in March, 2012 (Fig. 4).

Due to the failure of the basic treatment, the persistence of disease activity (BASDAI of more than 4, ASDAS according to CRP of more than 3.5) and systemic manifestations — frequent relapses iridocyclitis, presence of significant complications, a combination of cytotoxic drugs with genetically engineered biological drugs (GEBD) was recommended. Since 2012, the patient started therapy with GEBD (infliximab) in combination with disease modifying antirheumatic drugs (DMARD). From 2012 to 2015, therapy with Remicade 400 mg was performed once every 8 weeks. Tolerance is good, there was a decrease in clinical and laboratory indicators of disease activity (BASDAI less than 4, ASDAS for CRP — 1.5), in relapses of uveitis up to 1 time per year, the need for NSAIDs increased only 2–3 days before the subsequent injection of Remicade. In 2013, X-ray imaging of the joints revealed osteoarthritis of the left shoulder joint of the stage IV, TEP for this reason (Fig. 5).

Figure 3. *Scar after prosthesis of the left hip joint*

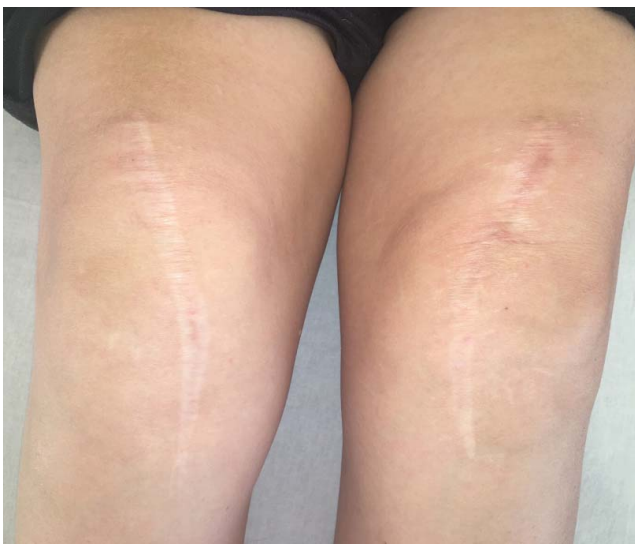

Figure 4. *Scars after prosthesis of the knee joints*

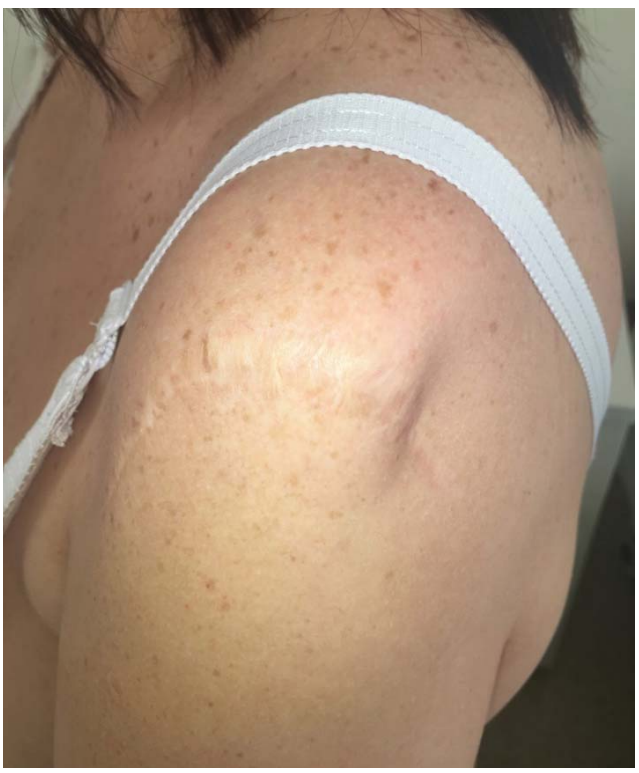

Figure 5. *Scar after prosthesis of the left shoulder joint*

From 2015 to 2017, due to the lack of Remicade, therapy with etanercept 25 mg per week was carried out. The effect was incomplete — clinically there was no need for NSAIDs, in the laboratory there was increase in activity indicators (ESR — up to 40 mm/h), exacerbation of uveitis — up to 4 times a year. With an increase in the dose of etanercept to 50 mg per week, a decrease in the activity of the process according to laboratory parameters to a low degree of activity was noted, but uveitis relapses still occurred up to 2 times a year.

From 2017 to the present time, the patient receives constant therapy with Remicade 400 mg injected once time every 8 weeks with a positive effect (BASDAI less than 4, ASDAS according to CRP — 1.3).

Discussion

This clinical case demonstrates some features of the course of uveitis in AS. First, attention is drawn to the onset of uveitis as a non-skeletal manifestation of the disease at a young age, secondary to inadequately treated arthritis, non-diagnosed spondylitis. For several years, no attempts to treat uveitis, to stop its progression were effective enough. Since the underlying disease was not verified, there was no appropriate therapy.

According to literature, uveitis is one of the most common non-skeletal manifestations of AS [13]. Despite the fact that the predominant form of uveitis in AS is iridocyclitis (anterior uveitis) and rarely involves the posterior parts of the eye with an immediate threat to vision, some patients may develop complications that lead to a significant decrease in visual functions. It is known that the frequency of complications correlates with the frequency of uveitis exacerbations: more than two attacks of uveitis per year, even without taking into account their duration and severity of inflammation, may be sufficient for the development of complications [13]. Thus, the main factor of the unfavorable prognosis of uveitis in patients with AS is a recurrent course.

An indicator of uveitis severity in AS is the need for GEBD administration: in accordance with the domestic recommendations for the treatment of AS, as well as the recommendations of the International Association of Ophthalmologists for the treatment of uveitis in SpA, recurrent uveitis is an indication for the administration of GEBD, and in most cases they have a positive effect on the frequency of uveitis exacerbations.

With the development and progression of the disease in the patient, who had not received adequate therapy for a long time, the most pronounced left-sided damage to the joints and eyes, namely, early complications in the form of severe uveitis of the left eye, which resulted in complete blindness, and severe secondary arthritis with the outcome in prosthesis of the left HJ, left knee joint, left shoulder joint were diagnosed.

Due to the late diagnosis of the underlying disease, there was also a late start of adequate therapy of both the AS and non-skeletal manifestations of the disease. In addition, the patient was characterized by low adherence to therapy, which significantly aggravated the progression of ankylosing spondylitis, and the severity of uveitis. To a certain extent, the turning point came after the beginning of therapy with GEBD: since that time, there has been a decrease in the activity of the disease, a decrease in the number of uveitis relapses.

This clinical case confirms the peculiarity of uveitis in patients with AS — in the absence of adequate therapy, including GEBD, uveitis is characterized by frequent relapses, occurring in one or both eyes, with the aggravation of the disease and the development of complications, significantly reducing vision in patients up to complete blindness.

Conclusion

In the diagnosis of AS and dynamic follow-up for patients, a thorough examination is necessary for the timely diagnosis of non-skeletal manifestations of the disease, including such common ones as uveitis. In turn, with the development and persistent recurrent course of uveitis, a thorough examination of the patient is necessary to identify rheumatic disease, including AS.

During both the onset of uveitis, and the onset of AS, there is need for diagnosis and examination by at least two medical specialists — a rheumatologist and an ophthalmologist, so that timely and correct diagnosis, as well as the high compliance of the patient promote early treatment of the

underlying disease and extra-skeletal ophthalmic manifestations, preventing the frequent recurrence of uveitis, reducing the risk of severe complications, which significantly reduce patients' quality of life.

Conflict of interests

The authors declare no conflict of interests.

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