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СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О КЛИНИКЕ И ДИАГНОСТИКЕ ПЕРВИЧНОГО ВАСКУЛИТА ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ

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Modern Concepts on the Clinic and Diagnosis of Primary Vasculitis of the Central Nervous System

Резюме

Первичный васкулит центральной нервной системы (ПВЦНС) — редкая форма васкулита неизвестной причины, поражающего сосуды головного, спинного мозга и мозговых оболочек без системного поражения. Установлено, что средний возраст начала заболевания приходится на 50 лет. Клинические проявления зависят от калибра пораженных сосудов. Наиболее частыми начальными симптомами являются головная боль и сосудистые когнитивные нарушения, что связано с поражением сосудов малого калибра. Развитие инсульта и очаговых симптомов взаимосвязано с сосудистыми когнитивными нарушениями и проявляется поражением средних/крупных мозговых артерий. Диагностика ПВЦНС затруднена, так как симптомы васкулита за пределами центральной нервной системы встречаются редко, серологические маркеры воспаления находятся в норме. Анализ спинномозговой жидкости обычно не соответствует норме из-за умеренного неспецифического повышения уровня общего белка или количества лейкоцитов. У 97 % пациентов с ПВЦНС выявляются отклонения от нормы (инфаркты, иногда опухолевидные поражения) по данным магнитно-резонансной томографии головного мозга. Ангиография имеет низкую чувствительность и низкую специфичность, так как позволяет верифицировать васкулит только средних и крупных церебральных артерий, выявляя сегментарные сужения. Для выявления воспаления кровеносных сосудов, а также для исключения других заболеваний необходимо выполнить биопсию вещества и мягких оболочек мозга.

Ключевые слова: *первичный васкулит центральной нервной системы, сосудистые когнитивные нарушения, головная боль, нейровизуализация, биопсия*

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Abstract

Primary vasculitis of the central nervous system (PACNS) is a rare form of unknown cause vasculitis that affects the vessels of the brain, spinal cord and meninges without systemic damage. It was found that the average age of the onset of the disease was 50 years. Clinical manifestations depend on the caliber of the affected vessels. The most common initial symptoms are headache and vascular cognitive impairment associated with small vessel involvement. The development of stroke and focal symptoms is interrelated with vascular cognitive impairment and manifests as the lesion of the middle/large cerebral arteries. PACNS is difficult to diagnose, since symptoms of vasculitis outside the central nervous system are rare, serologic markers of inflammation are normal. The analysis of cerebrospinal fluid is usually abnormal due to a moderate nonspecific increase in the level of total protein or the number of leukocytes. Deviations from the norm (cerebral infarction, sometimes tumor-like lesions) are detected according to the data of magnetic resonance imaging of the brain in 97 % of patients with PACNS. Angiography has low sensitivity and low specificity, since it allows to verify vasculitis of only middle and large cerebral arteries, revealing segmental narrowing. To detect inflammation of the blood vessels, as well as to exclude other diseases, it is necessary to perform a biopsy of the substance and the soft membranes of the brain.

Key words: *primary vasculitis of the central nervous system, vascular cognitive impairment, headache, neuroimaging, biopsy*

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ANCA — antineutrophil cytoplasmic antibody, DC — dendritic cells, MRA — magnetic resonance angiography, MRI — magnetic resonance imaging, CTA — computer angiography, PCNSV — primary isolated central nervous system vasculitides (angitis), RCVS — reversible cerebral vasoconstriction syndrome, ERS — erythrocyte sedimentation rate, CAA — cerebral amyloid angiopathy, CNS — central nervous system, CSF — cerebrospinal fluid

Introduction

Vasculitides is a heterogeneous group of diseases caused by an autoimmune vessel injury, characterised by vessel wall inflammation, necrosis, deformation and sclerosis, resuling in ischemic changes in organs and tissues, the blood to which is supplied by damaged vessels. These diseases is a rare pathology: the annual incidence is appoximately 4.2 cases per 100,000 people; however, the number of cases tends to grow globally. Vasculitides can be primary (the cause is unknown) and secondary (caused by infections, cancer and rheumatoid diseases). Currently, the Russian Federation does not operate any unified register of patients with this disease [1-9].

The nomenclature and classification of vasculitides were discussed by leading experts during the Chapel Hill Consensus Conference (CHCC) back in 1992. The first classification based on the vessel size was successfully used over two decades. Along with emergence of new knowledge and achievements in dynamically developing field of rheumatology, a new, up-to-date classification was needed. In 2010–2011, leading experts were discussing classification of vasculitides with the help of highly experienced clinicians (GPs, rheumatologists, nephrologists, immunologists) and anatomic pathologists, from over 50 leading medical centers in Europe, America, Australia, China, and Japan. Thus, the most complete new information on existing vasculitides was presented in the vasculitides nomenclature during the 2012 Chapel Hill Consensus Conference (CHCC2012) [5-8]. The Chapel Hill nomenclature is erroneously called a classification, since it does not contain diagnostic criteria; it contains information on various forms of vasculitides based on the diameter of an affected vessel (large, medium-size and small vessels), etiology and patogenetic features of the inflammatory process, that is why it is quite bulky and is not handy for everyday use in clinical practice [5-7].

The main objective of the nomenclature is to develop a unified interdisciplinary approach, to classify available information of the diseases. Taking into account available data on the practical use of the terms and the idea of disease manifestations, the name was reviewed, and main categories were isolated. For the first time this up-to-date nomenclature was updated with a new additional category of variable vasculitides affecting vessels of any size and type; vasculitides of a single organ was included into a separate category. This category included cutaneous leukocytoclastic angitis, cutaneous arteritis, primary central nervous system vasculitides (PCNSV), isolated aortitis (there are no signs of the possibility of a limited systemic variant) [5-8].

Early diagnosis of vasculitides is challenging because of non-specific initial presentations and numerous symptoms resembling other diseases (clinical masking symptoms) [9, 10]. For a majority of clinical entities of vasculitides, there are no specific laboratory tests or diagnostic methods for antibody-negative vasculitides; therefore, it is recommended that the disease is diagnosed with biopsy and pathomorphological examination of biopsy material; instrumental diagnostic tools

(cerebral angiography, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and computer angiography (CTA), high-resolution MRI (HR-MRI) [9, 11] can be used as well.

Something that seemed impossible several years ago has become available due to development of new instrumental diagnostic methods that can not only identify, but also describe the progress of a number of vasculitides (Takayasu disease, Kussmaul disease, etc.) [10]. A rare, hard-to-diagnose, severe single-organ vasculitides is primary central nervous system vasculitides (PCNSV) [1-4, 8, 9, 12, 13]. Depression in patients with PCNSV increases the near-term risk of death and possible suicide, deteriorates cognitive functions and the quality of life, reduces functional activity, hinders rehabilitation and recovery [12-14]. A large study by Hajj-Ali R.A. et al. (2019) assessed the long-term capabilities, quality of life and depression in patients (n = 27) with PCNSV during 5.5 ± 4.7 years, using Barthel Index (BI), European Quality of Life Questionnaire (EuroQol) and Patient Health Questionnaire, PHQ-9. The analysis demonstrated that 19 patients out of 27 were mildly disabled (70.4 %), while 5 patients had severe disability (18.5 %). 14 patients out of 27 (51.9 %) did not have any problems with independent movement, 18 patients (66.7 %) could cater for themselves, and 15 patients (55.6 %) did not experience any limitations in their daily life. Only 8 patients (29.6 %) in the study group did not have concerns, while 70 % showed minor signs of depression [14]. In the study by C. Salvarani et al. (2015) conducted over a 29-year period (from 1983 to 2011), the PCNSV mortality was observed in 25 patients (15 %) out of 163. Without therapy, patients with PCNSV died within a year, any subsequent recurrence increased the risk of death [15].

PCNSV affects vessels of any size in the brain, rarely spinal cord, and their lining, while vessels in other organs and systems remain intact. In scientific medical literature, the abbreviation "PCNSV" is also used for the following diseases: primary central nervous system (CNS) angitis, isolated CNS vasculitides (angitis) [12, 13, 16-18]. Despite the fact that over the last decade this clinical entity gained attention, it still rare and understudied.

Epidemiology

It is hard to determine the exact incidence of PCNSV in the population, since the disease has no specific clinical manifestations, specific serum inflammatory markers, while neuroimaging diagnostic methods return false-positive and/or false-negative results; there are no generally accepted international standards for prompt PCNSV diagnosis [8, 15-20].

PCNSV is one of the rarest forms of vasculitides, with the assumed incidence being 2.4 cases per 1 million people. In the 17-year-long study by Salvarani C., et al. (2017), PCNSV was diagnosed in 64 % of cases in the group of 114 patients vs. CNS disorders associated with other types of vasculitides or other rheumatic conditions [21]. The mean age of disease onset is approximately 50 years; however, PCNSV can develop in any age [21]. Usually PCNSV is described as a disease affecting middle-age men. Bernstein J.E. et al. (2020) found that PCNSV affects men of 40–60 years old [21]. In the study by Sundaram S. et al. (2019), the mean age of 45 patients (68.9 % were men) was 36 years [23]. However, according to the study by Salvarani C. et al. (2017), the retrospective analysis of a group of 163 PCNSV patients who were followed up by Mayo Clinic (Rochester, Minnesota, USA) during 29 years, demonstrated that women prevailed (n = 86, 56 %) [21]. This form of vasculitides is observed in paediatric population as well. Elbers J. et al. (2016) described PCNSV in boys (62–74 %) [24].

Etiology and Pathogenesis

Causes and mechanisms of PCNSV are understudied; however, it is well known that vessel wall inflammation is facilitated by genetic factors and infections (varicella-zoster virus, Epstein-Barr virus, versatile virus west nile virus, human immunodeficiency virus). These etiologic factors are merely triggers, i.e., they trigger the pathological pocess. Unfortunately, genetic factors have not been studied systematically; there are no evidences of hereditary disease, and reliable causes of PCNSV are still unclear [1, 8-9, 11-13, 16-20, 24].

Epidemiological factors trigger autoimmune pathogenetic mechanisms of PCNSV, associated with immune system activation and inflow of activated macrophages and T-cell (mainly T-helpers), that reinforce the immune response, to the vessel wall. Self-sustained failure of tolerance to vascular cells occurs, and an immune response develops against native components (autoimmune antigens), that serve as a target for T-effector cells, causing damage to the vessel cells containing these autoimmune antigens. The area of vascular damage contains numerous T-effector cytokines, that affect the functional activity of vessel cells and apoptosis — programmed cell death.

Vasculitides is caused by impaired cell-mediated immunity (development of delayed hypersensitivity reaction). Numerous scientific papers describe migration of macrophages and effector T-lymphocytes that form granulomas (macrophages surrounded by T-lymphocytes). In turn, active macrophages cause vessel wall degradation, thus intensifying the pro-inflammatory

activity of endothelium and leading to hyperplasia and lymphocytic infiltration of endothelial cells. All these pathological changes result in granulomatous inflammation and, later, necrotising angiitis [1, 8-9, 11-13, 16-20, 24]. Vessel wall intima which is not hyperplastic and fibrotic, causes vessel lumen to narrow; a new vascular tree appears and occlusion occurs, thus causing damage to the vessel wall and hemorrhage into adjacent tissues [1, 8-9, 11-13, 16-20, 24].

Diagnostic Criteria and Clinical Presentation of PCNSV

First criteria for a differential diagnosis of PCNSV were proposed and developed for small arteries in 1988 by Americal rheumatologists Calabrese L. and Mallek J. In order to diagnose PCNSV, all three criteria below need to be met:

1) " Neurologic impairment or mental deterioration that cannot be explained by any other causes"
2) " Typical angiographic signs (alternating areas of gradual artery dilatation or narrowing) or histopathologycal manifestations in the CNS"
3) "No signs of widespread vasculitis and other diseases that can cause symptoms or angiographic signs of vasculitides" [1, 8, 25, 26].

Late in the XX century, Calabrese L., Mallek J. introduced the term "reversible cerebral vasoconstriction syndrome" (RCVS), which has clinical and angiographic signs (alternating areas of vessel dilatation or narrowing) similar to signs of PCNSV. However, this condition is caused by an idiopathic vasospasm and not by intracranial vasculitides. Unlike PCNSV, this syndrome is benign and has good prognosis [8, 25, 26].

It is worth mentioning that introduction of angiography into clinical practice allowed diagnosing and differentiating vasculitides depending on the size of an affected vessel. However, angiography is useful for vasculitides of large and medium-sized arteries, while vasculitides of small arteries remain negative and can be verified only with contrast angiography [8, 13, 16, 26].

In 2005–2010, when brain imaging diagnostic methods (high-resolution MRI) were developed for vasculitides verification, inflammation could be identified by thickening and contrast enhancement of the artery wall.

When the informative value of MRI as a method for PCNSV diagnosis was analysed, it became obvious that this method was not less superior than histology in terms of the following criteria: sensitivity and specificity (80 and 100 %, respectively) [8, 13, 16, 26].

In 2009 Birnbaum J. and Hellmann D. proposed to differentiate between confirmed (a histological examination of a tissue biopsy sample) and possible PCNSV in the absence of biopsy, when the signs of vasculitides were found on an angiocardiogram, together with abnormal MRI scans and cerebrospinal fluid (CSF) results that correlated with inflammation [27].

The modern medicine uses diagnostic criteria for vasculitides of small arteries which were developed 30 years ago by a group of scientists led by Calabrese L. and Mallek J [25], for any vessel size. PCNSV does not have a pathognomonic clinical presentation. In the first large study by Sarti C. et al. (2020), which was a detailed overview of all available literature sources on PCNSV, the authors summarised all medical records (n = 585) published in the medical database of the US National Library of Medicine (2002–2019) and analysed the clinical findings [26]. They found out that, depending on the brain areas involved, PCNSV can present with various clinical symptoms (Figure 1). Sometimes, the onset of the disease can be epileptic seizures [26].

Moreover, the disease severity and the rate of progression can differ a lot, thus enhancing the non-specific nature of clinical manifestations. A majority of patients had several symptoms and syndroms at a time [8, 21, 28-31].

Clinical symptoms depend on a various degree of pathology of the brain, or spinal cord, or meningeal layer: reduced lumen (stenosis or occlusion); segmental increase or decrease in the vessel diameter; formation of aneurysms with subsequent vessel wall rupture and hemorrhage into adjacent structures [8, 13, 16, 17, 26, 28].

The severity of the above symptoms depends on the diameter of the affected vessel. Very often cognitive disorders can be a first sign of PCNSV. More marked cognitive disorders are typical of PCNSV with small vessel involvement [8, 21, 29].

Salvarani C et al. (2017) and de Boysson H. et al. (2017) draw attention to the fact that in small artery vasculitides, vascular cognitive disorders are by 67–71 % more frequent and by 36–47 % more severe vs. involvement of large and medium-sized arteries. It was found out that vascular cognitive disorders in patients with PCNSV progressed within a month, sometimes within a week [21, 29]. In the study by Sundaram S. et al. (2021), where 45 patients with suspected PCNSV were examined, 19 patients had their diagnosis confirmed with high-resolution vessel wall imaging (HRVWI). Images evaluation revealed involvement of large (n = 13), medium-sized (n = 16), and small (n = 11) vessels, while cognitive impairment was observed in 5 patients (25 %) and was considered a poor prognosis [32].

In patients with PCNSV, cognitive disorders are often accompanied by mental and affective disorders: emotional instability, aggression, irritability, misinterpretation of own and other peoples' actions, sudden abandonment of an activity, confusion [33].

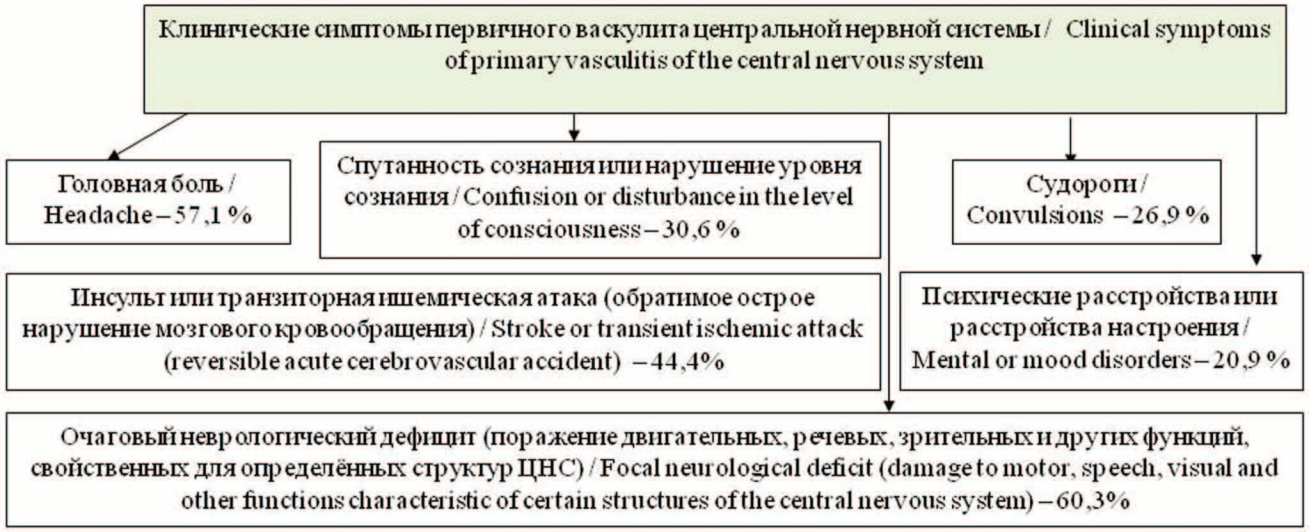

Figure 1. *Main clinical symptoms PVCNS*

The article by de Boysson H. et al. (2017) studied and compared clinical features of PCNSV in 102 patients. 26 patients (25 %) presented with isolated involvement of small vessels, 76 patients (75 %) had damage to their medium-sized/large vessels [29]. It was found out that small artery PCNSV is observed more frequently at a young age (41.5 years old) compared to medium-sized/large vessel PCNSV (48.5 years old), p = 0.04 [29]. 46 patients (45 %) had speech pathology, 22 patients (22 %) had mental disorders [29].

It was noted that in isolated small vessel involvement, as opposed to the involvement of medium-sized/large vessels, the following clinical symptoms were more common: epileptic seizures (n = 20; 77 %) vs. (n = 16; 21 %), p < 0,0001, dyskinesia (n = 9; 35 %) vs. (n = 7; 9 %) p = 0,002. In turn, where medium-sized/large vessels were damaged, 67 patients (88 %) had focal neurologic impairment: palsy, sensory or atrophic disorders (p = 0.0002), 64 patients (84 %) had stroke (p < 0.0001), 16 patients (21 %) suffered from insomnia (p = 0.03), 11 patients (42 %) had dizziness (p = 0.07) [29]. Headaches were observed in patients with damages to vessels of any size. Therefore, since headache (51–65 %) is one of the most common complaints in general and can be a sign of a number of neurological disorders, the features of headache which can help in suspecting PCNSV should be taken into account. Investigators often describe headache as subacute or chronic headache that starts unnoted; it is dull, diffuse, sometimes intermittent, intensifies with time, sometimes resembles migraine, or varies in severity, usually mild to moderate [34, 35]. Patients who already have headaches describes it as something different from the pain they used to have. In turn, in rare tumour-like PCNSV (5 %, mean age: 37 years old) caused by damage to small vessels, headache can be acute, severe and can be accompanied by vomiting and neurological disorders (epileptic seizures in 90 %) [26, 34, 36]. Clinical manifestations are a result of edema that presses the structures adjacent to the brain. Very often this form of PCNSV is confused with a tumour or lymphoma, therefore, prompt diagnosis of tumour-like PCNSV is difficult. Thunderclap headache is rarely observed in patients with PCNSV, and it helps differentiating it from other neurological disorders that can resemble its clinical presentation, for instance subarachnoid haemorrhage or reversible cerebral vasoconstriction syndrome [25, 26, 34, 37].

According to N.A. Totolyan et al. (2013), the diagnostic value of the clinical manifestations of PCNSV was considered in the following categories: headache (especially persistent, atypical, with meningeal or hypertensive manifestations, with specific onset time) — very high value (+++); step-wise progressing multifocal (mainly subcortical) neurological dysfunction syndrome, including cognitive disorders, disrupted innervation, pseudobulbar syndrome, bilateral pyramidal-extrapyramidal dysfunction with gait disturbance, pelvic disorders — high value (++) [9].

In the clinical practice, there are the following rare PCNSV variants: isolated spinal vasculitides (with frequent thoracic section involvement, 5 %), vasculitides with signs of hemorrhage, vasculitides with amyloid deposits [20, 38, 39, 40]. It is worth mentioning that the elderly patients (mean age: 65 years old) have this pathological peptide depositing in small arteries of the cortex, in the arteries of the meninx vasculosa and meninx serosa with the immune response to beta amyloid.

Table 1. The course of PPCNS depending on the caliber of the affected vessel

Small arteries	Large arteries
Progressive, long severe course	Monophasic, with the development of a fatality

Patients with this condition demonstrate high incidence of cognitive disorders (71 %) and a high risk of parenchymatous hemorrhage (20 %) [38, 39, 40]. The course of PCNSV depends on the size of a damaged vessel (Table 1).

According to de Boysson H et al. (2018), 10 % of patients with PCNSV had an instant poor course of the disease represented by impaired wakefulness and development of respiratory disorders (shortness of breath) [20].

Rarely there can be common symptoms evidencing a multisystem disease, such as fever (14 %), weight loss, rash, peripheral neuropathy, arthritis, and night sweats that were observed in 20 % of patients [15, 29]. Where these symptoms are present, secondary CNS vasculitides needs to be ruled out.

Diagnostic Features

Diagnostics is based on the above criteria (Calabrese L. and Mallek J., 1988) [25]. Irrespective of the achivements in the studies of PCNSV, making diagnosis is challenging due to the lack of highly sensitive and specific diagnostic tests. Laboratory tests, brain imaging and histopathology are useful methods both for confirmation of suspected PCNSV and for ruling out of other conditions with similar manifestations [1, 8-9, 11-13, 16-20, 24].

Laboratory Diagnostics

Usually, laboratory test values are within the reference range. In some cases, blood tests can demonstrate signs of system inflammation: anemia, leucocytosis, high platelet count, high ESR [33, 41]. 27-33 % of patients have increased acute phase protein (C-reactive protein) pointing out to an inflammation [33, 41]. In rare occasions, patients present with a diagnostically insignificant increase in specific blood markers: cytoplasmic antibodies (ANCA) and antinuclear antibody (autoimmune antibody that can damage the wall of small vessels) [8, 14, 42].

Cerebrospinal fluid (CSF) demonstrates abnormalities in 80–90 % of patients. According to Salvarani C. et al. (2015), an increased protein concentration is the most common laboratory finding. In a group of patients (n = 101), a mean CSF protein concentration was 7 g/L (range: 1.5–10.3 g/L) [15]. High pressure is observed in 50 % of patients, while higher lymphocyte count can be recorded in 50–80 % [8, 15, 29]. Lymphocytic pleocytosis of CSF is moderate and is rarely higher than 250 cells/μL [8, 14, 15, 29]. A higher WBC count and the presence of neutrophils are uncommon; if present, they should warn about a possible infection [8, 42, 43].

In the retrospective analysis conducted by Shuster S. et al. (2017) in 31 patients (mean age: 45.6 years old), PCNSV was diagnosed only in 17 patients (55 %) using biopsy and in 14 patients (45 %) — with the help of high-resolution MRI. A group of investigators led by Shuster S. et al. (2017) found out that the CSF composition depends on the diameter of a damaged vessel. The following feature can be observed when analysing CSF: when small vessels are involved, cytosis (16 cells/μL) and protein (98 mg/dL) are present, while in case of medium-sized/large vessel involvement, these values tend to decrease four-fold (cytosis: 4 cells/μL, protein: 56 mg/dL) [8, 42].

These values show that the pathological process is highly active, and they need to be measured in order not to overlook similar diseases (infections: varicella-zoster virus, hepatitis C and B, syphilis, human immunodeficiency virus, TB; autoimmune: exanthematous lupus erythematosus, rheumatoid arthritis; malignancies), due to the lack of specific PCNSV markers [8, 14-15, 41-43].

Currently, biomarkers that make it possible to diagnose PCNSV in blood serum and CSF are being searched for. Special attention is paid to the role of immune mechanisms (T- and B-cell immunity, cytokine storm) in development of inflammation in the vessel wall. There is a limited number of studies dedicated to the role of dendritic cells (DC) in the adventitia and media of medium-sized and large arteries in various diseases and pathological conditions where the immune system is involved. Normally, the vessel wall is intact to the exposure by the immune system (it is not destroyed as a foreign tissue), but only with defective DC caused by pathological DC stimulation by Toll-like receptors. During this process, the vessel wall undergoes DC structure alternation, DCs grow in number, resulting in activation of T-cell inflow to the vessel wall via vasa-vasorum. Besides, a lot of effector cytokines can be found where a vessel is damaged (IL-6/IL-17 or IL-12/IFN-γ clusters), and they take part in steady inflammation sustention in the vessel wall [44-46].

However, a complex assessment of the impact of these immune mechanisms (T-cell immunity and cytokines) on the development of the inflammation in patients with PCNSV has not been performed. This new area (vascular immunology) is described just in single papers. T. Ruland et al. (2018) assessed T-lymphocite population in blood and CSF samples taken from 2 study groups.

Group 1 are the patients (n = 4) with PCNSV and large vessel involvement, where the diagnosis was made on the basis of clinical symptoms, cerebral angiography and MRI, and by ruling out a system inflammation. Controls were patients (n = 4) with idiopathic intracranial hypertension. Blood and CSF samples of patients with PCNSV demonstrated reduced CD3+ T-cell count vs. controls (p = 0.029). No other changes in T-cell population were found [47].

In the study by T. Ruland et al. (2018), A4-amyloid beta (APP) levels in CSF of patients with PCNSV were low. Proceeding from the results, the authors assume that its absence/low values in CSF of patients with PCNSV (451.44 ± 196.21 ng/mL) vs. controls (1513.7 ± 255.55 ng/mL); t = 5.61, p = 0.0000641, can be a marker of brain damage in PCNSV [47].

The study by Strunk D et al. (2018) evaluated the cell composition of CSF of 18 patients with PCNSV confirmed with brain biopsy (n = 4) and cerebral angiography (n = 14). It was found out that an increase in the lymphocyte count in CSF correlates with the brain biopsy results (lymphocytic infiltration) [48]. It is worth mentioning that the authors made the following assumption: immune cells in CSF can characterise the immune process in the CNS. In addition to the increase in the lymphocyte count in CSF, 33 % of patients had antibody-releasing cells, due to intrathecal Ig G synthesis. Therefore, this area needs further investigation, as the pathological role of T- and B-cell immunity and cytokines should be verified in larger cohorts [48].

A promising PCNSV marker in CSF is interleukin-17 (IL-17). IL-17 is a pro-inflammatory cytokine and a potent cell immunity mediator. Deb-Chatterji M (2019) et al. reported that the level of IL-17 produced by CD4+ T-cells in CSF was higher than normal in patients with PCNSV (sensitivity: 73 %, specificity: 100 %). Continuously increased IL-17 levels were observed in patients with active PCNSV and remission, evidencing that IL-17 is a more specific PCNSV biomarker that the number of cells and/or increased CSF protein and has crucial significance in the pathogenesis of this disease. These results tested in large cohorts will allow developing new therapeutic humanized anti-IL-17 antibody drugs for the management of PCNSV [49].

The circulating immune complex (CIC) is detected in blood with the help of immunomagnetic isolation or flow cytometry. Deb-Chatterji M (2019) et al. demonstrated that CIC values were increased significantly in patients with active PCNSV, but decreased with successful use of immunodepressants. Therefore, these results have a potential to facilitate diagnosis of cases with negative biopsy results and to monitor successful use of immunodepressants; however, further studies in larger number of patients are required [49].

Cerebral Angiography

Many clinicians use cerebral angiography as a tool of choice for diagnosing PCNSV due to a relatively low risk compared to brain biopsy. The main angiographic diagnostic criterion for vasculitides is multifocal, continuous or intermittent stenosis with areas of dilated vessels. This imaging pattern is not always specific, since it can be observed in other pathological processes: vessel wall spasm and/or edema, emboli in cerebral vessels; therefore, correct PCNSV diagnosis requires correlation with clinical and laboratory data [8, 13, 15-18, 21, 26]. It is worth mentioning that angiographic results show the typical signs of PCNSV more often in the damage to medium-sized/large vessels, compared to involvement of small vessels, because of low angiographic resolution [8, 13, 15, 16].

Raghavan A. et al. (2019) compared two methods (cerebral angiography and brain biopsy) in 128 patients (mean age: 49.8 years old) with PCNSV. It was found out that only 5 patients (21.74 %) out of 23 patients with confirmed biopsy results had typical angiographic presentation of PCNSV. Also, examination of 70 patients with negative biopsy results demonstrated that only 46 patients had typical angiographic changes [50].

Disadvantages of the practical use of this method include extreme invasiveness. This examination in not recommended in patients with renal disorders, because the contrast dye is toxic. Therefore, an improvement in this method with a better image quality and higher resolution will allow detecting inflammatory changes even in small arteries [1,8-9, 13, 15-17].

Brain Imaging

Patients with suspected PCNSV undergo a mandatory MRI assessment of the changes in their brain substance, cerebral blood flow assessment using magnetic resonance angiography (MRA) and computer angiography (CTA), contrast assessment of the vessel wall using high-resolution MRI (HR-MRI) [1, 8-9, 11, 13, 15-17, 28].

Changes in the brain substance detected by MRI are non-specific and are more common in the damage to medium-sized/large arteries. The bed of a damaged vessel shows single or multiple foci (hypointense in T1 and hyperintense/heterogeneously changes in T2 or FLAIR); where the contract medium is used, it accumulates suing a cerebrovascular accident. In turn, in small vessel vasculitides, various variants can be observed: multiple brain infarctions in both cerebral hemispheres, irregular areas of subcortical vasogenic edema (hyperintense in T2 or FLAIR, isointense in T1), parenchymatous hemorrhage (8 to 55 %) [8, 11, 15]. In the study by Schuster S. et al. (2017), brain substance examination

revealed atrophy in cortical and subcortical structures, caused by transmural inflammation of small arteries confirmed with biopsy. Contrast uptake by cerebral meninges is observed more commonly in small vessel vasculitides compared to the damage to large vessels (60–77 % vs. 22–29 %) [8, 42].

It is worth mentioning that pseudotumor PCNSV is a rare pathology (approximately 15 %) and its diagnosis is challenging. In contrast brain imaging, this condition resembles other pathologies, such as malignancies, pseudoneoplasms or brain abscesses [8, 12, 15].

According to Charidimou A. et al. (2017), 12 % of patients have tumour-like foci [51]. A distinctive brain imaging evidence of A-β-associated angitis which allows distinguishing cerebral amyloid angiopathy (CAA) is contrast uptake by meninx vasculosa with or without infiltrative changes (70 % vs. 7 %) and rare lobar hemorrhage (7 % vs. 62 %) [39]. In the study by Salvarani C. et al. (2015) 80 patients out of 149 patients with PCNSV had brain infarctions (in medium-size/large artery involvement — 66 %, in the damage to small arteries — 34 %) [21]. In another study by Schuster S. et al. (2017), brain MRI revealed a typical pattern of brain infarction in the damage to medium-size/large arteries (85.7 %) vs. small vessel involvement (29.4 %). Therefore, MRI is a highly sensitive method (95–100 %), but possesses low specificity, and the vessel bed needs a MRA assessment [42].

It is worth mentioning that MRA and CTA images show areas of even or mildly uneven stenosis intermitting with delated areas, in one or several arteries, vessel abnormalities (single or multiple stenoses and/or occlusions) [8, 11, 13, 15-17].

MRA allows for comprehensive assessment of the vessel wall, while CTA is better in identifying the rate of stenosis and blood flow and a bypass network. In turn, the practical application of MRA and CTA in small vessel involvement is impossible due to the lack of angiographic changes. Thus, these methods have low specificity compared to the traditional contrast cerebral angiography [8, 30, 42].

Previously described methods do not make it possible to distinguish between inflammatory and non-inflammatory vasculopathies. In order to differentiate PCNSV from other/non-inflammatory vasculopathies, the vessel wall is now examined with contrast enhancement in HR-MRI dark-blod-fat-sat mode (fat and blood psychic inhibition), allowing to improve imaging [8, 12-13, 15-18, 35]. The key differentiator in PCNSV is smooth, concentric and segmental thickening of the vessel wall with contrast uptake and perivascular edema [8, 15, 29, 42]. Noh H. et al. (2016) noted that contrast uptake allows diagnosing PCNSV at an early stage of the pathologic process, when cerebral angiography is inefficient [30]. Besides, this phenomenon allows differentiating from atherosclerotic vascular disease, since unlike PCNSV, an atherosclerosis plaque is eccentric, with local vessel wall thickening without any signs of perivascular edema, and the contrast uptake depends on its composition (from moderate to high intensity) [8, 12-13, 15-18, 35, 42]. This method will be developed further and its resolution will improve in the clinical practice, thus making in possible to diagnose inflammation of small arteries.

Brain Biopsy

Currently, the golden diagnostic method for PCNSV is still brain biopsy, however, it successfully diagnoses histopathological abnormalities only in 50–75 % of cases [13]. Since cerebral angiography is inefficient in the damage to small arteries (the results are negative), brain biopsy is one of the most useful verification methods [14, 15, 25].

Very often cerebral vessel biopsy yields little information, in 50 % of cases it is false-negative, if a sample is taken from an unaffected area in case of focal and/or segmental involvement. Therefore, a single negative biopsy result does not rule out PCNSV. In order to reduce the false-negative results rate, the following additional methods are used: MRI to search for an abnormality in an expected damage area; leptomeningeal test (the diagnostic level increases to 87 %). In a majority of cases, biopsy is performed for differentiation from widespread vasculitis (either autoimmune or infectious), non-inflammatory vasculopathies (reversible cerebral vasoconstriction syndrome) or malignancies (lymphoproliferative disorders) [8, 23, 29].

Morphologically, PCNSV is divided into three most common histopathology variants: granulomatous vasculitides, lymphocytic vasculitides, necrotising vasculitides (Figure 2). Mixed variants are observed as well. Histological patterns remain stable over time, therefore, it can be assumed that these patterns do not correspond to various disease stages [12-13, 15-18, 24].

Morphological changes in PCNSV are noted in medium-sized arteries and arterioles. Damage to veins is uncommon (the endothelium remains intact); there are rare cases of isolated medium-size alba vein involvement [51]. The study by Mlakar J et al. (2016) describes for the first time a case report of PCNSV with granulomatous vein inflammation (phlebitis) in a 22-year-old woman manifesting with acute headache. Biopsy sample morphology demonstrated vasculocentric mononuclear infiltration associated with well-defined granulomas and/or multinucleated giant cells through the vessel wall [8, 52].

β-A4 amyloid deposits are common in granulomatous vasculitides, but are not unique for this type,

therefore, biopsy is required for differentiation from cerebral amyloid angiopathy (CAA). A distinctive histological feature making it possible to differentiate between CAA and PCNSV is perivascular inflammatory response (infiltration with mono- and polynuclear cells), where granulomas are not typical [8, 39-41, 52].

The incidence of lymphocytic vasculitides comes second among histopathological variants of PCNSV; its manifestations include marked lymphocytic inflammation with sparse plasma cells, usually in several layers. Necrosing vasculitides is the rarest variant; its manifestations include transmural fibrinoid necrosis, that resembles nodular polyarteritis. The development and progression of necrosing vasculitides result in intracerebral bleedings and microaneurysms (12 %). In PCNSV, brain biopsy samples demonstrate ischemia in 40–51 % of cases [8, 12, 13, 16, 18].

The paper by C. Salvarani et al. (2015) includes the results of a retrospective analysis of 163 patients with PCNSV who underwent assessment in Mayo Clinic in 1983 to 2011. Upon admission, patients presented with various neurological symptoms (headache, cognitive disorders, etc.). PCNSV was diagnosed if brain or spinal biopsy samples demonstrated transmural destructive inflammatory infiltrate in the artery wall, if there were segmental narrowing of the smooth artery wall, cerebral artery dilatation or occlusion in the absence of any changes in artery wall typical of atherosclerotic vascular disease.

A follow-up examination allowed excluding patients with the signs of system disorders (exanthematous lupus erythematosus and other) and infection. The patients did not have a history of exposure to vasoactive substances, migraneous or thunderclap headaches. The endpoint of the clinical study was death of the patient or last hospitalisation (mean follow-up: 12 months, range: 0–13.7 years). During the 12-month follow-up, 81 patients out of 163 patients with PCNSV had their brain or spinal cord biopsy taken. Following biopsy, PCNSV was diagnosed only in 58 patients (72 %). Biopsy sample analysis demonstrated the following histopathological variants: granulomatous vasculitides in 34 patients (59 %) (deposition of beta amyloid in vessel wall in 20 patients (34 %)); lymphocytic vasculitides — in 13 patients (22 %); necrotising vasculitides — in 10 patients (17 %); a mix of granulomatous and necrotising vasculitides was observed in 1 patient [15].

In turn, 105 patients had their PCNSV diagnosed with the help of cerebral angiography, including 82 patients who initially did not undergo biopsy. 23 patients who did not have any signs of vasculitides in their biopsy material presented with vasculitides in angiography [15].

Despite the fact that brain and meninx biopsy is the golden standard for diagnosing PCNSV and that it possesses high specificity, its sensitivity is not sufficient enough and makes 53–63 % and 50–70 % according to various sources [8, 13, 14].

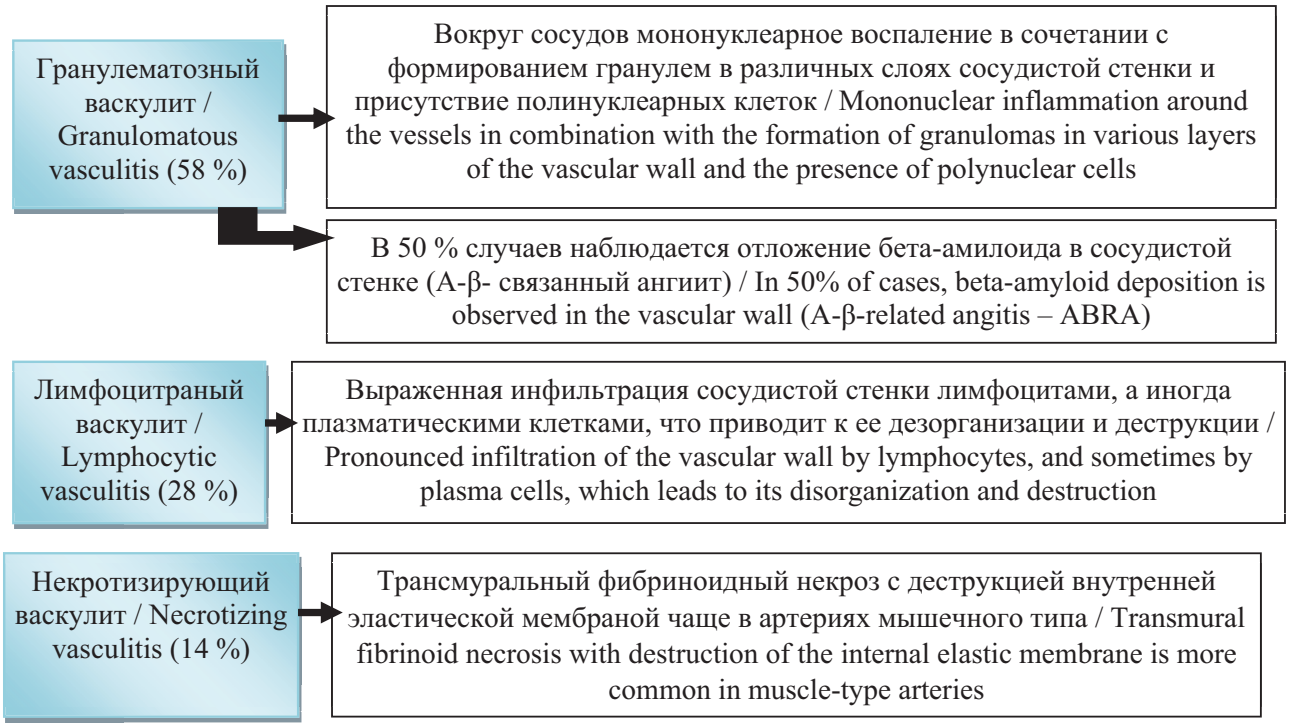

Figure 2. *Histopathological variants of PVCNS*

Conclusion

Despite the new knowledge of clinical presentation and diagnostic methods of PCNSV, this form of vasculitides remains understudied. Early identification of such non-specific common clinical presentations of PCNSV as headache, cognitive dysfunction and long-lasting neurological disorders (transient ischemic attack, aphasia, seizures, ataxia, sharp hemiparesis, semi-sensory loss, loss of fine motor skills, hemifacial weakness, etc.), will help in timely identification of patients with suspected disease, referral to clinical and laboratory tests, instrumental examinations, including brain biopsy. Untimely diagnosis of PCNSV will result in patient disability and/or death within a year. A major part of patients with PCNSV cannot work or experience challenges in professional life. PCNSV development and progression cause cognitive disorders, depression, anxiety, resulting in the reduction of quality of life of patients and their families. Taking into account the lack of specific blood and CSF markers, and also non-specific nature of cerebral angiography; limitations in the use of brain imaging methods (changes in brain substance during MRI, assessment of the cerebral blood flow during magnetic resonance angiography (MRA) and computed angiography (CTA), contrast high-resolution MRI (HR-MRI) of the vessel wall); challenges with the use of brain biopsy as a routine method due to its highly invasive nature.

Despite these limitations, a clinical diagnosis needs to be made in every individual case, even if it is a suspected or controversial diagnosis, and laboratory and instrumental assessments need to be performed in order to rule out/confirm PCNSV.

Currently, some ongoing clinical trials investigate triggers and pathogenetic mechanisms of a pathological process in the vessel wall in PCNSV. It may happen that in future specific and sensitive biomarkers of vessel wall damage will be found and will be used for the development of new diagnostic algorithms or to improve the verified diagnostic criteria of PCNSV.

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ЛЕЧЕНИЕ ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА И САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Treatment of Patients Chronic Coronary Heart Disease and Type 2 Diabetes Mellitus

Резюме

Сочетание хронической ишемической болезни сердца и сахарного диабета 2 типа у пациента имеет высокую медицинскую значимость и привлекает к себе растущее внимание мирового врачебного сообщества. Серьезные изменения, произошедшие в лечебной тактике у пациентов, имеющих сочетание ишемической болезни сердца и сахарного диабета 2 типа, требуют пристального внимания. Современные подходы к терапии этой группы пациентов включают в себя направления, улучшающие сердечно-сосудистый прогноз (изменение образа жизни, прием антитромботических препаратов, антигипертензивной терапии, гиполипидемических средств — статинов и нестатиновых гиполипидемических препаратов (которые показаны пациентам, тяжело переносящим лечение статинами), сахароснижающих препаратов), а также внимательное ведение синдрома стабильной стенокардии (прием антиангинальных средств, оценка возможностей реваскуляризации). Новая линия сахароснижающих препаратов обладает высокими кардиопротекторными свойствами, снижает интенсивность поражения сосудистого русла (вазопротекция), оказывает ренопротекцию. Стратегия выбора сахароснижающих препаратов претерпела ряд изменений и в данный момент обозначается, как «дифференцированная», что подразумевает необходимость выбора препарата с наибольшими органопротективными свойствами. Достижение целевых уровней гликированного гемоглобина (HbA_{1C}) в границах 7,0-8,0 % ассоциировано с наименьшим уровнем смертности пациентов. Кроме того, пациентам с сахарным диабетом 2 типа, в особенности имеющим ишемическую болезнь сердца, рекомендовано свести к минимуму эпизоды развития гипогликемических состояний. Данное сообщение ставит перед собой задачу подробно обсудить основные подходы к ведению пациентов с ишемической болезнью сердца и сахарным диабетом 2 типа, а также подходы к улучшению сердечно-сосудистого прогноза.

Ключевые слова: *ишемическая болезнь сердца, сахарный диабет 2 типа, сердечно-сосудистые заболевания, сердечно-сосудистый прогноз*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The combination of chronic coronary heart disease and type 2 diabetes mellitus in a patient has high medical importance, because relevance of the problem increases every year. Modern requirements for the provision of high-quality medical care to patients with combined pathology require attentive assessment: we can't deny the pathophysiological relationship of both diseases. Serious changes that occurred in the treatment tactics in relation to such patients require close attention of the medical community. Modern approaches of the therapy of this group of patients include treatment directions that improve the cardiovascular prognosis (lifestyle changes, anti-platelet therapy, antihypertensive therapy, statins and nonstatin lipid-lowering agents, which are indicated for patients who are difficult to tolerate statin treatment, glucose-lowering drugs), as well as careful management of stable angina syndrome (using of antianginal drugs, assessing the possibilities of revascularization). The therapeutic tactics of the new revision offers promising perspective regimens for taking antiplatelet therapy, lipid-lowering drugs. The new line of glucose-lowering drugs has high cardioprotective properties, reduces the intensity of vascular lesions (vasoprotection), and has renoprotective properties. The strategy of choosing glucose-lowering drugs has also undergone some changes: at the moment it is designated as «differentiated», which implies choosing a drug with the highest organoprotective properties. Achievement of target HbA1C levels in the range of 7.0-8.0 % is associated with the lowest patient mortality rate. In addition, to patients with type 2 diabetes mellitus, especially group with coronary heart disease, advised to minimize episodes of hypoglycemic conditions. Aim of this statement is to discuss in detail progressive approaches in the treatment of patients with chronic coronary heart disease and type 2 diabetes mellitus.

Key words: *coronary heart disease, type 2 diabetes mellitus, cardiovascular diseases, cardiovascular prognosis*

Conflict of interests

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AH — arterial hypertension, BP — blood pressure, CABG — coronary artery bypass graft, ACE — angiotensin converting enzyme, GLP-1-RA — glucagon-like peptide-1 receptor agonist, ASA — acetylsalicylic acid, CCB — calcium channel-blocking agent, DAPT — dual antiplatelet therapy, DNP — diabetic nephropathy, CHD — coronary heart disease, DPP-4i — dipeptidyl peptidase-4 inhibitor, MI — myocardial infarction, SGLT-2i — sodium-glucose linked transporter-2 inhibitor, CA — coronary artery, LV — left ventricle, HDL — high density lipoproteins, LDL — low density lipoproteins, OMT — optimal medical therapy, T2DM — type 2 diabetes mellitus, HF — heart failure, TG — triglycerides, EF — ejection fraction, PCI — percutaneous coronary intervention, HbA_{1C} — glycated hemoglobin, β-ABs — β-adrenoblockers, ω3-PUFA — ω3-polyunsaturated fatty acids

Introduction

The issue of concomitant coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) is of high social significance, attracting increasing attention of the global medical community. In spite of existing separate Guidelines for each of these conditions, which are subject to regular update, in 2020, the experts of the American Heart Association (AHA) published a scientific statement, defining the principles of treatment of patients with stable CHD and T2DM. Due to close pathophysiological relationship between CHD and diabetes mellitus, some experts raise the question about the inevitability of coronary involvement in T2DM. In recent years, there have been major changes in the views on the treatment strategy for this patient group; additional promising administration schedules have been proposed for antithrombotic and lipid-lowering agents; glucose-lowering agents with persuasive cardio-, vasoprotective and renoprotective effects have emerged. At the same time, in many cases, the actual state of medical care for patients with CHD and diabetes mellitus does not meet modern requirements. For example, according to the data from the latest EUROASPIRE V registry, a large proportion of these patients do not receive necessary cardioprotective agents, and the frequency of reaching target blood pressure (BP), cholesterol (C), and glycated hemoglobin (HbA_{1C}) is "far from the desired" [1].

This publication is aimed at discussing modern approaches to the treatment of patients with chronic CHD and T2DM. When considering these issues, the authors used both the AHA scientific statement mentioned above and other modern guidelines [1, 2].

Approaches to improve cardiovascular prognosis

Change in lifestyle

Lifestyle changes, including smoking cessation, rational diet, slimming, control of psycho-emotional stress, and moderate physical activity, are cornerstones for the treatment of patients with both T2DM and CHD.

Smoking cessation is an urgent measure for all patients with T2DM, regardless of CHD presence. Diverse adverse cardiovascular effects of smoking have been clearly demonstrated. In patients after myocardial infarction (MI), smoking is associated with a significant (51 %) increase in the risk of recurrent MI [3]. Smoking cessation significantly reduces coronary risk, reaching the nonsmoker levels–about three years after cessation.

Favorable effects of smoking cessation do not depend on the presence of T2DM. Smoking cessation can be accompanied by a moderate weight gain (about 5 kg), which can be considered a problem for some patients. It has been shown that such increase in body weight, even in persons with T2DM and obesity, does not affect the extent of cardiovascular risk reduction achieved by smoking cessation [3].

A rational, balanced, and healthy diet is considered as "the cheapest and natural" approach to reducing the clinical manifestations and the rate of T2DM progression and its microvascular and macrovascular complications. When dietary advice is implemented in practice, the extent of HbA_{1C} reduction is similar to or even greater than that achieved on medical treatment; adherence to a healthy diet significantly reduces the need for expensive drug products. In the primary prevention trial PREDIMED (7447 patients at high cardiovascular risk, of whom 3614 had T2DM), the use of the Mediterranean diet led to a 30 % reduction in the risk of composite endpoint, including cardiovascular death, MI, and stroke; this beneficial effect did not depend on the presence of diabetes mellitus [4]. The choice of food products may be based on the bread unit count, which is widely presented in special tables. It is considered necessary that the diet of patients with T2DM should contain an increased quantity of vegetables and fruit (primarily non-starchy), dietary fiber, legumes, vegetable proteins, unsaturated fats, and nuts, while reducing the consumption of processed meat products (sausages, etc.). It is recommended that the use of refined carbohydrates and sweet drinks should be minimized. Practical implementation of the developed dietary recommendations is a long and complicated process. In case of patient adherence, the change in food preferences may take at least 2–8 months. To enhance the chances of success, the given advice should be flexible; explanations should be easy to understand, and the willingness to repeat attempts should be guaranteed. The physician's time, personal involvement, and sympathy to the patient are essential conditions for dietary plan implementation [4].

An important component of the nonmedical advice for many patients with T2DM and CHD (especially those with arterial hypertension [AH] and/or diabetic nephropathy [DNP]) is the reduced use of kitchen salt (<5 g of sodium chloride a day). This amount of salt is fairly well tolerated, has no adverse biological effects, helps reduce BP, reduces the risk of cardiovascular complications, slows the rate of renal involvement progression, increases organic protective effect of renin-angiotensin-aldosterone system blockers, and increases the effect of diuretic therapy. It is important to explain to patients that by observing dietary salt restriction, the individual taste perception threshold also decreases within 4 to 6 weeks, and, subsequently, a low-salt diet becomes quite comfortable [5].

Control of psycho-emotional stress and sleep disorders Epidemiological data (REGARDS, ADDITION trials) are suggestive of a distinct relationship between macrovascular complication of T2DM (including MI, stroke, need for revascularization, and limb amputation) with signs of depression and psychosocial distress. The mechanisms of this association are still unclear; the effect of correction of these disorders on the course of CHD and T2DM also requires clarification.

Sleep disorders, which are often closely associated with obesity, have been identified as an adverse factor to be controlled in diabetic patients. Their association with sympathetic nervous system hyperactivity, pro-inflammatory reactions, and endothelial dysfunction has been demonstrated. Correction of obstructive sleep apnea has a favorable impact on the BP levels and a number of positive cardiometabolic effects. Other sleep problems, including its insufficient duration, can be accompanied by adverse effects on the lipid profile, insulin resistance, and vegetative balance, which is very important for patients with concomitant T2DM and CHD [6].

Regular graduated exercise in patients with T2DM helps reduce the levels of blood sugar, BP and inflammatory markers, normalize body weight, improve lipid profile parameters and muscle strength, reduce the tendency to depression, improve quality of life, and have a favorable effect on the prognosis. A lot of patients and diabetes mellitus and CHD are prone to sedentary lifestyle. The current guidelines on the management of patients with concomitant T2DM and stable CHD include (1) while being awake, a prolonged resting state should be interrupted every 30 minutes with light physical activity and (2) cumulatively, maintaining at least 150 minutes of moderate or significant physical activity per week as a necessary element of treatment strategy [7, 8].

Slimming is an important component of T2DM and CHD treatment in obese patients. The main approaches include a low-calorie diet (usually 1200–1500 kcal/day for women and 1500–1800 kcal/day for men, with an energy deficit of about 500 kcal/day), increased physical activity, and changes in eating habits and behavior. During the controlled slimming, the initial goal is the loss of 5 %–10 % of body weight over 6 months. In rare cases, when these approaches appear to be ineffective, medical therapy and bariatric surgery (usually, in patients with body mass index ≥35–40 kg/m^2) [8, 9].

Antithrombotic agents

Currently, T2DM is considered as generalized hypercoagulable state. Hyperglycemia and hyperinsulinemia, which are typical of diabetes mellitus, have adverse effects on the vascular endothelium, interrupt atheroprotective NO-dependent regulatory mechanisms, contribute to the formation of proinflammatory and vasoconstrictor effects, cumulatively favoring atherothrombosis. T2DM is associated with a number of platelet receptor apparatus defects, dysregulation of their adhesion functions, activation and aggregation, increased destruction and decreased duration of platelet existence, a relative increase in the number of large immature platelet forms in circulation. Expectations regarding blocking of prothrombotic effects of DM are related to the evolution of antithrombotic agents, emergence of their more powerful representatives, and introduction of more advanced therapeutic regimens [10].

Acetylsalicylic acid (ASA) and clopidogrel

Treatment with antiplatelet agents is a fundamentally important component of secondary prevention in patients with T2DM; by reducing the thrombogenic potential, they reduce cardiovascular risk. DM-related abnormalities of the platelet receptor apparatus can lead to a decreased response to treatment with ASA (75–100 mg/day) and dual antiplatelet therapy (DAPT) with clopidogrel (75 mg/day), which is even more pronounced in concomitant DNP with impaired renal function. Some authors suggest increasing in frequency of administration and/or the dose of antiplatelet agents (e.g., ASA 75 mg twice daily) as one of the measures to overcome this effect; however, the safety of such alternative regimens needs to be confirmed. In some patients with T2DM and stable CHD (in the absence of stenting or MI within the last year), administration of clopidogrel alone in the standard dose instead of ASA may be justified (in the randomized controlled trial (RCT) CAPRIE, clopidogrel was significantly superior to ASA, reducing the risk of ischemic complications without a significant increase in bleeding risk: as in the whole of 19,185 patients with an increased cardiovascular risk as in the subgroup of 3866 patients with diabetes mellitus). Another strategy variant, which may be considered for patients with T2DM and chronic CHD, is the longer-than-usual DAPT (ASA in combination with clopidogrel) [10]. AHA experts consider it possible to recommend this approach to patients at very high cardiovascular risk (e.g., with prior MI, of younger age, smokers), balancing the risk of ischemia and bleeding. To facilitate decision-making, the calculator proposed by R.W. Yeh et al. can be used: (1) 1 point for current cigarette smoker, for diabetes mellitus, for current MI, for prior MI or coronary stenting, for paclitaxel-eluting stent, for stent diameter <3 mm; (2) 2 points for clinical manifestations of heart failure or left ventricular (LV) ejection fraction (EF) <30 %, for vein graft stent; (3) 0 points for age <65 years, 1 point for age 65–74 years, 2 points for age ≥75 years; (4) consideration of the total score: the score of ≥2 points are in favor of long-term use of DAPT [10].

Table. *Calculator ischemia-bleeding risk balance for deciding on long-term dual antiplatelet therapy (adapted by R.W. Yeh et al.)*

Parameters	Score
Smoker	1
Diabetes mellitus	1
Myocardial infarction	1
Post myocardial infarction or coronary stents	1
Paclitaxel-eluting stents	1
Stents diameter <3 mm	1
Clinical manifestations of heart failure	2
Ejection fraction of left ventricular <30 %	2
Stenting of venous shunt	2
Age	
– <65 years	0
– 65-74 years	1
– ≥75 years	2

Note: The presence of ≥2 points indicate in favor of long-term use of DATT

Ticagrelor

The possibility of using this drug product has been expanded based on the data from the large THEMIS RCT presented in 2019. In the trial, the efficacy of ASA alone was compared to a combination of ASA and ticagrelor (60 mg twice daily) in 19,271 patients with T2DM and CHD but without history of MI or stroke. Over 40 months of follow-up, the balance between decreased cardiovascular risk and increased bleeding risk was favorable only for a predetermined group of patients who had previously undergone coronary stenting procedures. It is this category of patients that may benefit from this treatment strategy, provided the risk of bleeding is low [11].

Rivaroxaban

Another opportunity for secondary prophylaxis in persons with T2DM and chronic CHD, in the absence of high risk of bleeding, could be a combination of ASA with a low dose of a new oral anticoagulant: rivaroxaban, an inhibitor of coagulation factor Xa. It is ¼ of the dose that is routinely used for antithrombotic prophylaxis in atrial fibrillation. In a large-scale COMPASS RCT (27,395 patients with chronic CHD not requiring standard DAPT), treatment with ASA in combination with rivaroxaban 2.5 mg twice daily significantly reduced the risk of cardiovascular complications compared to ASA, at the cost of increased risk of nonfatal bleeding. A favorable effect on the cardiovascular prognosis in patients

with T2DM was less pronounced than in patients without DM [12].

Experts of the European Society of Cardiology (ESC) classify all variants of long-term treatment with ASA in combination with other antithrombotic agents as IIa/A and IIb/A at high and moderate levels of cardiovascular risk, respectively, and in the absence of a high risk of bleeding, reserving this approach mainly for postinfarction patients who have already been receiving DAPT for at least 1 year [9].

Platelet function assay Despite the initial enthusiasm concerning the possibility of improving approaches to the choice of antithrombotic strategy in patients with chronic CHD using the evaluation of platelet function, serious RCTs have not been able to confirm these expectations yet [6].

Antihypertensive therapy

The prevalence of arterial hypertension (AH) in patients with T2DM is twice as high as that in the general population. Not less than 70 %–80 % of patients with diabetes mellitus are reported to have AH. Arterial hypertension in T2DM patients is associated with an additional increase in the risk of MI, stroke, and overall mortality. Epidemiological studies demonstrate a steady increase in the incidence of microvascular and macrovascular events in patients with diabetes mellitus with increasing levels of systolic BP above 115 mm Hg [13].

Target blood pressure levels

The issue of BP levels that are considered desirable to provide organ protection and improve prognosis in individuals with AH both in general and in certain categories of patients (the elderly, with diabetes mellitus, with chronic CHD, etc.) has long remained debatable, which created some confusion in the target BP values recommended by different medical associations. This was due to the fact that large RCTs and registries demonstrated contradictory data on the effects of more intensive BP lowering: either negative (INVEST, CLARIFY, ONTARGET, TRANSCEND, ACCORD) or positive (SPRINT). Currently, both Russian experts and leading world communities (American Heart Association, European Society of Cardiology, International Society of Hypertension) share opinion that the most suitable BP levels for the majority of patients with T2DM and chronic CHD may be 120–129 mm Hg (130–139 mm Hg for the age >65 years) systolic and 70–79 mm Hg diastolic [14].

Choice of antihypertensive agents

Angiotensin-converting enzyme inhibitors (ACE) and sartans have traditionally been recognized as the main variants of AH control in patients with diabetes mellitus and CHD, and to improve cardiovascular prognosis (HOPE, EUROPA, VALIANT and other RCTs and their subanalysis) and slow the progression of decline in kidney function. Beneficial effects of these classes of drug products on prognosis are particularly pronounced in postinfarction patients and in those with impaired left ventricular systolic function. Since the vast majority (up to 70 %) of patients with T2DM and AH required >1 therapy, the issue of adequate combination selection is of special importance. It is considered that the most acceptable addition to ACEs and sartans would be dihydropyridine calcium channel blockers (CCBs) and thiazide-like diuretics (indapamide, chlorthalidone). The opinion on thiazide diuretics is less conclusive: their adverse effect on insulin sensitivity, insulin secretion and ability to worsen glycemic control is well known. However, taking into account beneficial effect on cardiovascular prognosis, in serious RCTs (ALLHAT), their use is considered possible [14]. In recent years, there have been active discussions on the possibility of using mineralocorticoid receptor antagonists (spironolactone, eplerenone), which are quite effective in patients with resistant AH and can improve cardiovascular prognosis in patients with impaired LV systolic function. β-adrenoblockers (β-ABs) are mainly reserved for diabetic patients with clinical manifestations of angina, LV EF <40 %, postinfarction patients, and those with cardiac rhythm disturbances. Among the drug products of this class, the preference is given to medications with vasodilating properties (carvedilol, nebivolol), the metabolic side effects of which are less pronounced. The combined hypotensive therapy for T2DM and chronic CHD can also include (if necessary) centrally acting agents (moxonidine and urapidil), α-adrenoblockers (doxazosin), and long-acting nitrates [14, 15].

Lipid-lowering agents

Proatherogenic lipid changes associated with T2DM largely contribute to increased cardiovascular risk. The most typical of them are increased levels of triglycerides (TG), small large particles of low-density lipoprotein cholesterol (LDL-C), apolipoprotein C-III, lipoprotein Lp(a), and decreased levels of high-density lipoprotein (HDL) cholesterol. Persistent hypertriglyceridemia and hyperglycemia contribute to oxidation and glycation of LDL-C particles, thus increasing their atherogenicity. The listed lipid shifts contribute to the formation and progression of endothelial dysfunction, promote proinflammatory and prothrombotic effects, accelerate the development of atherosclerotic vascular disorders. The important role of lipid disorders in prognosis worsening in patients with T2DM is evidenced by data from serious RCTs on a pronounced reduction in the cardiovascular risk on

treatment with medications affecting dyslipidemia activity. In 2020, data from a meta-analysis of 52 RCTs on the assessment of leading lipid-lowering agents: statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 enzyme (PCSK9) inhibitors were published; the analysis included only studies with ≥1000 patient-years; a total of 327,037 patients were included in the analysis. A decrease in LDL-C by 1 mmol/L was shown to be associated with a reduction in the risk of cardiovascular events by 19 %; this effect did not depend on the baseline level of LDL-C (including the baseline levels of 2.0 mmol/L), the used class of lipid-lowering agents, presence of diabetes mellitus or chronic kidney disease [16, 17].

Target levels of LDL-C

When using lipid-lowering agents, it is advisable to strive for achieving target LDL-C levels. According to the European Society of Cardiology experts, for patients with chronic CHD and T2DM, the target levels are (1) <1.8 mmol/L or a 50 % reduction from baseline for high-risk patients; (2) <1.4 mmol/L or a 50 % reduction from baseline for very high-risk patients; (3) and <1.0 mmol/L for patients who have had ≥2 cases of cardiovascular events over the last 2 years [18].

Statins

The use of statins in addition to lifestyle changes play an important role in the primary and secondary prophylaxis of CHD in patients with T2DM. Compared to individuals without diabetes mellitus, in patients with T2DM, the use of statins leads to similar lipid-lowering effects and an equal (or even greater) positive effect on the cardiovascular prognosis in patients with T2DM (RCTs HPS, TNT, JUPITER, etc.).

For patients with chronic CHD and T2DM, current guidelines recommend the choice of high-intensity statin therapy (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day, these doses provide a reduction of LDL-C by ≥50 % versus baseline), and if there are factors limiting their use, such as age >75 years, the use of moderate-dose statins is recommended. It should be noted that if muscle side effects of statins develop, their use in very low doses (less than the standard minimum, e.g., atorvastatin 5 mg every other day) is considered possible, recognizing that statins can have a certain degree of organ protection [19].

Several RCTs and their meta-analyses have demonstrated that statins are associated with a small but statistically significant increase in the risk of T2DM. The level of this risk is lower than that associated with the use of thiazide diuretics and non-vasodilating β-ABs. However, it is most important that the cardiovascular protective effects of statins significantly outweigh the increased risk of diabetes mellitus associated with their use. It has been demonstrated that one additional case of T2DM can develop when treating 255 people with statins for 4 years. Over this time, 5.4 cases of cardiovascular events can be prevented. The analysis that included 9 RCTs (a total of 9696 patients) has shown that in patients who already have diabetes mellitus, an increase in the levels of HbA_{1C} associated with the use of statins is rather moderate and amounts to 0.12 % over 3.6 years. Therefore, it is important that physicians understand and convince their patients that, in spite of a slight increase in glycemic levels that accompanies administration of statins, the risk/benefit ratio for this group of drug products clearly favors their use in patients with T2DM (and its risk factors) in combination with CHD [20, 21].

Non-statin lipid-lowering agents

Although statins play a leading role in the secondary prophylaxis in patients with T2DM and CHD, some patients do not tolerate high doses due to side effects or fail to achieve the desired levels of LDL-C necessary to reduce the cardiovascular risk. In these patients, it is reasonable to use alternative lipid-lowering agents in addition to statins. Among these lipid-lowering agents, ezetimibe and PCSK9 inhibitors are the most commonly used, while fibrates, nicotinic acid preparations and ω3-polyunsaturated fatty acids (ω3-PUFAs) are less common [19].

In a large-scale IMPROVE-IT RCT (including a total of 18,144 patients with acute coronary syndrome (ACS),4533 of them having T2DM), ezetimibe, an intestinal cholesterol absorption inhibitor, in combination with statins demonstrated an additional decrease in LDL-C and improvement of cardiovascular prognosis; these effects appeared to be more pronounced in patents with T2DM than without [13].

In recent RCTs: FOURIER (27,564 patients with atherosclerotic cardiovascular disorders, 11,031 of them with diabetes mellitus) and ODYSSEY OUTCOMES (18,924 patients with a recent experience of ACS, 5444 of them with T2DM), PCSK9 inhibitors such as evolocumab and alirocumab in combination with statins showed an effective reduction in LDL-C and a pronounced positive effect on cardiovascular prognosis. These favorable changes did not depend on the presence of diabetes mellitus [22, 23].

The international experts have used the data from the three RCTs mentioned above as the grounds to support "the lower, the better" concept in respect of the relationship between the LDL-C levels and the cardiovascular risk (some experts suggest modifying the concept name with the same aphoristic connotation: "lower, faster, younger", without an explicit lower threshold of proven benefit). Currently, some experts consider LDL-C concentrations that are unusually low for routine cardiological practice,

such as <1.0 mmol/L (and even <0.65 mmol/L) to be desirable for individuals with extremely high cardiovascular risk (including those with T2DM, peripheral artery lesions, recent MI, history of recurrent cardiovascular events). It is emphasized that the existing evidence of long-term safety of such low concentrations of LDL-C are still limited and require additional confirmation. In general, it is considered that ezetimibe and/or PCSK9 inhibitors are indicated to the patients with T2DM and CHD in addition to statins, provided the LDL-C levels on the treatment with maximum tolerated doses of the latter are maintained at the level of ≥1.4 mmol/L [17].

Several RCTs studied the opportunities to lower the cardiovascular risk under the influence of other lipid-lowering agents, used in addition to statins. In these studies, fibrates, nicotinic acid preparations, and various representatives of ω3-PUFAs failed to demonstrate distinct favorable cardiovascular effects, which led to a significant weakening of the position of these drug products in primary and secondary prophylaxis strategies. The use of fibrates and ω3-PUFAs in patients with T2DM and CHD is reserved for the cases with pronounced hypertriglyceridemia (1.5–5.6 mmol/L according to the European guidelines) to reduce the risk of pancreatitis [18, 24].

The data from REDUCE-IT RCT (8179 patients with atherosclerotic cardiovascular disorders, including 4730 patients with T2DM, who had TG levels of 1.5–5.6 mmol/L) can be a significant recent addition to the possibilities of lipid-lowering therapy. In this RCT, icosapent ethyl in the dose of 2 g twice daily showed a clear reduction of cardiovascular risk. This drug product (it is emphasized that the obtained results should not be extrapolated to other variants of ω3-PUFAs) are currently considered as the first-line therapy in patients with T2DM and CHD, provided the TG levels in these patients remain at a level of >1.5 mmol/L, according to ESC guidelines, in spite of the use of the maximum tolerated dose of statins and lifestyle changes [18, 25].

Lipid-lowering agents and cognitive function

Previous concerns about cognitive function deterioration on treatment with statins and other lipid-lowering agents are currently recognized as not supported by substantial evidence; therefore, these concerns should not prevent physicians from prescribing these drug products for appropriate indications [13].

Use of glucose-lowering agents

Intensive glycemic control was earlier considered to be the leading principle for reducing the risk of complications in patients with T2DM, including coronary events. The treatment strategy (referred to as ***glucocentric***) was primarily focused on the achievement and maintenance of target HbA_{1C} levels; no preferences to any glucose-lowering agents were given [1]. However, a number of RCTs later showed no improvement in cardiovascular prognosis in patients with T2DM with intensive glycemic control (with HbA_{1C} reduction to <6 %–6.5 %) compared to standard control. Moreover, several studies showed that glucose-lowering agents of various classes have a different effect on cardiovascular prognosis despite similar glycemia reduction. This led to the transformation of glycemic control strategy in T2DM into a ***differential*** one, giving preference to glucose-lowering agents with proven organic protective properties [26].

Target glycemic levels in patients with T2DM and chronic CHD

Although more intensive glycemic reduction with achievement of relatively low (6.5 %–7.0 %) HbA_{1C} levels is associated with a reduced risk of microvascular complications of T2DM (retinopathy, nephropathy, peripheral neuropathy), and, possibly, the risk of stroke, it is not related to a reduction in overall mortality, cardiovascular mortality and the incidence of cerebral stroke while maintaining the specified HbA_{1C} values. The largest RCTs (UKPDS, ADVANCE, ACCORD, VADT) did not show significant differences in the incidence of cardiovascular events in groups with more intensive glycemic control (mean HbA_{1C} 6.4 %–7.0 %) compared to groups where the control was less intensive (HbA_{1C} levels 7.3 %–8.4 %). Epidemiological studies and registries also suggest that the association between HbA_{1C} levels and mortality in patients with T2DM and cardiovascular disorders is U-shaped, where the lowest mortality rates correspond to HbA_{1C} values between 7.0 % and 8.0 %. These data were reflected in current guidelines of leading world endocrinology and cardiology associations, stating that

(1) HbA_{1C} levels 6.5 %–7.0 % can be used as target levels mainly in patients with T2DM who have sufficiently long-life expectancy and do not have significant comorbidities, DM complications, or episodes of severe hypoglycemia;

(2) HbA_{1C} levels of 7.0 %–8.0 % are more suitable for older patients with T2DM who have a moderate life expectancy, microvascular and macrovascular complications of DM, episodes of severe hypoglycemia, significant comorbidities; these particular values of HbA_{1C} are recommended by experts as target for the majority of patients with T2DM and chronic CHD;

(3) HbA_{1C} levels of 8.0 %–8.5 % may be considered as target for a limited category of most severe patients with T2DM who have limited life expectancy, pronounced microvascular and macrovascular complications of DM, severe comorbidities (end-stage renal, respiratory or heart failure, pronounced dementia, incurable cancer lesions) [27].

Risk of hypoglycemia

Several RCTs showed a 2–3-fold increase in the risk of pronounced hypoglycemia in patients with T2DM whose treatment provided for more intensive control of HbA_{1C}. Adverse effects of these episodes are not limited to the known combination of clinical signs; its sequelae include falls, injuries, road accidents, coma, and death. Moreover, the patients with concomitant cardiovascular disorders, episodes of hypoglycemia are associated with an increased cardiovascular risk, although the nature of this relationship requires further studies. For this reason, it is recommended that episodes of hypoglycemia in patients with diabetes mellitus, especially those with cardiovascular disorders (including CHD) should be minimized [28].

Sulfonylureas and insulins

Taking into account the high coronary risk typical of diabetes mellitus, as well as the wide differences in the mechanisms of action of the available glucose-lowering agents, the issue of the possible presence of special cardioprotective properties of certain classes of drug products is very important.

Cardiovascular safety of sulfonylurea derivatives has previously raised concerns among clinicians. The mechanism of glucose-lowering effect of these drug products involves membrane depolarization of pancreatic β cells with increased insulin release. Sulfonylurea-associated hyperinsulinemia, increased risk of hypoglycemia and impaired ischemic preconditioning were considered as factors that could potentially increase the cardiovascular risk. However, although the use of these drug products was associated with some increase in the risk in several retrospective epidemiological analyses, in the majority of large-scale controlled trials, their use (especially second-generation drugs such as glimepiride in the CAROLINA RCT) with respect to cardiovascular prognosis was quite neutral. in the UKPDS RCT, sulfonylurea derivatives demonstrated a reduction in the risk of microvascular complications of T2DM (especially of retinopathy and DNP [29].

For the same reasons as sulfonylureas, insulin preparations have previously been considered as ambiguous with regard to cardiovascular safety. The epidemiological studies of insulin preparations noted an increase in the cardiovascular risk; at the same time, the need for careful interpretation of these results is emphasized, since these drug products are usually reserved for a more severe category of patients. In the RCTs, the use of insulin preparations was accompanied by a reduced risk of microvascular complications of DM; their effect on the cardiovascular prognosis was neutral.

The available data allow the experts to consider careful use of sulfonylureas and insulin in patients with T2DM and chronic CHD, but not as first-line glucose-lowering therapies. This is all the more important because glycemic control products with proven favorable cardiovascular effects are already available to the physician [30].

Metformin, unlike sulfonylureas and insulin preparations, may have a positive effect on cardiovascular prognosis (UKPDS RCT), its use does not increase the risk of hypoglycemia and body weight. There is an ongoing large-scale RCT with prolonged used extended-release metformin (VA-IMPACT, 7868 patients with pre-diabetes and atherosclerotic cardiovascular disorders); the results are expected in 2024. Current guidelines on the treatment of patients with diabetes mellitus still consider metformin as the first-line glucose-lowering therapy and the most popular in patients with T2DM and chronic CHD in the developed countries [30].

Thiazolidinediones, due to their ability to increase insulin sensitivity ("insulin sensitizers "), were initially considered as promising therapies for persons with T2DM and CHD. Further, some ambiguous data concerning the effect of this class a representative (rosiglitazone) on cardiovascular prognosis provided the basis for alarming preliminary conclusions and limitations to their use. Although the results of representative RCTs (PROACTIVE, 5238 patients; IRIS, 3876 patients, with pioglitazone, and RECORD, 4447 patients, with rosiglitazone) in patients with T2DM and atherosclerotic cardiovascular disorders demonstrated favorable or neutral effects; practicing physicians still express some doubt regarding their use. These drug products may induce sodium and water retention, and thus deteriorating clinical signs of heart failure (HF). They are contraindicated for patients with chronic HF, and should be used with care in patients with CHD without HF [31].

Dipeptidyl peptidase-4 inhibitors (DPP-4i)

The controversial nature of the data on the effect of thiazolidinediones on cardiovascular risk is one of the reasons why the world's leading regulatory agencies, the US Food and Drug Administration, and the European Medicines Agency have made a decision not to authorize new blood glucose-lowering agents without conclusive evidence of cardiovascular safety in large RCTs. The first class of drug products subject to these studies were DPP-4i. These drug products increase the levels of endogenous incretins, elevate the production of insulin, and reduce glucagon release. The degree of the glucose-lowering effect of DPP-4i is lower than for the drug products listed above, but they do not increase the risk of hypoglycemia, do not increase body weight, and are well-tolerated. Representative RCTs of DPP-4i in the patients with T2DM demonstrated neutral effects on cardiovascular and renal

prognosis: (1) SAVOR TIMI-53 (16,492 patients, saxagliptin); (2) EXAMINE (5380 patients, alogliptin); (3) TECOS (14,671 patients, sitagliptin); (4) CARMELINA (6979 patients, linagliptin) [32].

Sodium-glucose linked transporter-2 inhibitors (SGLT-2is) were the first class of glucose-lowering agents that demonstrated an apparent beneficial effect on the cardiovascular and renal prognosis in patients with T2DM. These drug products increase glucose excretion in urine (≥100 g/day, which results in glycemia decrease), induce natriuretic, diuretic action and a complex of additional (pleiotropic) effects. Their use is associated with a moderate reduction in HbA_{1C} (by 0.3 %–0.6 %), systolic and diastolic BP (by 3–4 and 1–2 mm Hg), weight loss (by 2–3 kg). An increased risk of genital mycotic infections in both genders is reported among side effects, which is associated with glycosuria induced by their administration. Standard hygiene measures (daily shower) can help reduce the risk of these infections, and successful management of most manifested cases can be achieved through the use of topical antifungal agents. A positive effect of some representatives of SGLT-2is on the cardiovascular prognosis with a significant reduction in the rate of hospitalizations for heart failure, a decrease in cardiovascular and overall mortality was demonstrated for patients with T2DM and atherosclerotic cardiovascular disorders in RCTs: (1) EMPA-REG OUTCOME (7020 patients, empagliflozin); (2) EMPEROR-REDUCED (3730 patients, empagliflozin); (3) CANVAS (10,142 patients, canagliflozin); (4) DECLARE TIMI-58 (17,160 patients, dapagliflozin). Renoprotective effects (decrease in albuminuria, decrease in the rate of progression to end-stage renal failure and decrease in death from renal causes) have also been shown for all these drug products [33–36].

Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are mainly used as subcutaneous injections (only one of GLP-1-RAs — semaglutide — has an oral dosage form). These drug products, similar to DPP-4i, influence the incretin system and stimulate glucose-dependent insulin release by pancreatic islet cells; they also slow gastric emptying and reduce appetite. Side effects of GLP-1-RAs include dose-dependent gastrointestinal events (nausea, vomiting, diarrhea); injection site reactions (hypersensitivity reactions) are also possible. The use of GLP-1-RAs is associated with a more significant decrease in HbA_{1C} levels and weight loss compared to DPP-4i and SGLT-2i. In several large-scale RCTs, drug products of this class demonstrated beneficial effects on cardiovascular prognosis in the patients with T2DM with atherosclerotic cardiovascular disorders or a high risk thereof: (1) LEADER (9340 patients, liraglutide); (2) SUSTAIN-6 (3297 patients, semaglutide); (3) REWIND (9901 patients, dulaglutide); in AWARD-7 RCT, dulaglutide also demonstrated its renoprotective effects [37–39].

Taking into account the data from numerous RCTs, the experts state that the choice of a hypoglycemic agent is of great importance. Some glucose-lowering agents provide proven cardio-, vaso-, and renoprotection and are already considered to be preferable in the updated guidelines of the national and world medical associations (endocrinologists, cardiologists, nephrologists). In particular, GLP-1-RAs and SGLT-2i for which cardioprotective effects have been demonstrated are considered the glucose-lowering agents of choice (usually in combination with metformin) for patients with T2DM who have a high cardiovascular risk (including CHD). If a patient has apparent clinical signs of HF, the preference should be given to SGLT-2i. The same class also has benefits for patients with DNP at the levels of glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 (at the same time, the GLP-1-RA representative, dulaglutide can be used at GFR > 15 mL/min/1.73 m^2) [38, 40, 41].

Diagnostic approaches in a patient with stable angina

The use of most non-invasive and invasive investigation methods in patients with chronic CHD (including electrocardiography, echocardiography, exercise ECG/Echo ECG testing, radionuclide methods, coronary arteriography) do not depend significantly on the presence or absence of diabetes mellitus. Several recent trials (SCOT-HEART, PROMISE) demonstrated that in patients with T2DM and chronic CHD, coronary computed tomographic angiography compared to cardiac exercise stress tests can better diagnose nonobstructive coronary lesions and, due to this, improve the quality of medical treatment [42].

Antianginal therapy

In spite of the use of modern cardio- and vasoprotective medical therapies, as well as revascularization methods, clinical signs of angina are found in about 1/3 patients with stable CHD. Patients with T2DM and clinical signs of angina often have more common and severe coronary events compared to patients with patients without DM, which can be a restriction for revascularization [43].

Choice of antianginal agents

Drug products (1) that increase myocardial oxygen supply (nitrates, CCBs) and (2) that decrease myocardial oxygen consumption (β-ABs, CCBs, ivabradine, trimetazidine, ranolazine) can be used to relieve angina. Current

national and foreign guidelines provide for the use of β-ABs and/or CCBs, reserving other classes of antianginal agents for the cases of resistance or lack of effect of the first-priority drugs. In patients with stable CHD (in the absence of recent MI and heart failure), there is no convincing evidence that any of the above classes of antianginal agents can reduce the risk of MI and mortality; moreover, their effects on angina severity and exercise tolerance are considered to be very similar. In this regard, the choice of antianginal agents in people with T2DM should be primarily guided by their effects on BP and pulse rate, the nature of side effects, cost, and influence on glycemic levels. Approaches to the choice of a specific class of these drug products in patients with stable angina and diabetes mellitus are largely standard. As in patients without T2DM, it should be borne in mind that the use of nondihydropyridine CCBs in patients with LV systolic dysfunction and in those receiving β-ABs is undesirable. For long-acting nitrates, it is important to consider the risk of resistance and endothelial dysfunction in the absence of an adequate nitrate-free interval during long-term use [42].

Many representatives of β-ABs are effective antianginal agents and have metabolic side effects. β-ABs reduce the heart rate and myocardial contractility, therefore, reducing its oxygen demand. Compensatorily, this induces vasoconstriction, which, in turn, increases insulin resistance and leads to the formation of atherogenic lipid profile. β-ABs that have additional vasodilator effects (carvedilol, nebivolol) have either a favorable or neutral effect on metabolic parameters. In comparative studies in patients with T2DM, vasodilating β-ABs compared to non-vasodilating representatives of this class demonstrated a small but significant decrease in HbA_{1C} (by 0.1 %–0.2 %), improved insulin resistance, decreased cholesterol levels, weight loss, and slower rate of microalbuminuria development [31].

Among antianginal agents used in patients with T2DM, ranolazine, a selective inhibitor of the cardiomyocyte sodium channels, has been well studied. In addition to an effective reduction in angina activity, it influences glucagon secretion, which is accompanied by a decrease in HbA_{1C} levels by about 0.5 %–0.7 %. Both antianginal and glucose-lowering effects of ranolazine are more pronounced in patients with poorly controlled diabetes mellitus [44].

In patients with T2DM, combination antianginal therapy can include ivabradine and trimetazidine. Their antianginal activity does not depend on the presence of diabetes mellitus. Both drug products are metabolically neutral and have no influence on BP. Ivabradine is only used in patients with sinus rhythm; it can cause clinically significant bradycardia; in the presence of left ventricular systolic dysfunction, it has a beneficial effect on cardiovascular prognosis. Trimetazidine has no effect on the heart rate; it is contraindicated for patients with Parkinson disease and restless leg syndrome [42].

Revascularization opportunities

In patients with T2DM and CHD, treatment is based on optimal medical therapy (OMT includes the above-mentioned approaches to prognosis improvement and antianginal agents, if necessary) in combination with lifestyle changes. However, the importance of revascularization approaches increases together with increasing severity and prevalence of coronary events. The outcomes of surgical and transcutaneous revascularization in patients with T2DM are worse compared to patients without DM, including a higher risk of peri-procedural complications and coronary restenosis. The benefit/risk balance for each of revascularization approaches varies and depends on peculiarities of coronal anatomy, comorbidities and some other factors, thus requiring an individual approach to treatment strategy. In patients with multivessel stenosis, left main coronary artery involvement, complex coronal anatomy, coronary artery bypass grafting (CABG) compared to percutaneous coronary intervention (PCI) is associated with a decreased incidence of long-term major cardiovascular events (RCTs: BARI 2D, COURAGE, FREEDOM) with a slightly increased risk of stroke in the early period (the incidence of stroke within the first 30 days is 1.8 % after CABG, 0.3 % after PCI). The lower incidence of cardiovascular events post CABG may be related to greater completeness of coronary revascularization achieved in this intervention [43–46].

Summing up the data from RCTs conducted in recent years, the experts of American Heart Association and European Society of Cardiology note that the main indications for coronary revascularization in patients with T2DM in addition to OMT include (1) insufficient control of clinical manifestations of ischemia despite OMT; (2) the presence of widespread myocardial ischemia; (3) significant stenosis of left main coronary artery or proximal lesion of left anterior descending coronary artery. If coronary revascularization is indicated to a patient with T2DM, optimal approaches in addition to OMT are PCI via radial access and new generation coated stents, or CABG with shunt implantation preferably from the left a. thoracica interna (internal mammary artery). When selecting a revascularization method, individual approach, taking into account the state of coronal anatomy (SYNTAX index, etc.), cardiovascular risk profile, character of clinical manifestations and patient's preferences, is required for persons with multivessel coronary artery disease, left main coronary artery involvement, proximal stenosis of left anterior descending coronary

artery, multiple comorbidities, and decreased LV EF. Herewith, it is important to understand that the combination of OMT and CABG is the most beneficial for prognosis improvement in the majority of patients with diabetes mellitus and the above-mentioned peculiarities [47–50].

To conclude the discussion, let us emphasize the multidisciplinary nature of the issue of concomitant CHD and T2DM A decision on treatment strategy requires involvement of several medical specialists: cardiologist, endocrinologist, cardiovascular surgeon, probably, nephrologist, etc., with mandatory consideration of currently accepted national and international guidelines. The use of an integrative approach, including education of patients and their relatives, adequate changes in lifestyle, BP control, prescription of modern antithrombotic and lipid-lowering agents, differential choice of glucose-lowering agents with cardioprotective potential, weighted use of antianginal and revascularization methods will improve the quality of life and cardiovascular prognosis in the patient group under discussion.

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СРАВНЕНИЕ РЕЗУЛЬТАТОВ КТ ОРГАНОВ ГРУДНОЙ КЛЕТКИ ПРИ ПНЕВМОНИИ, ВЫЗВАННОЙ COVID-19, И ГРИППОЗНОЙ ПНЕВМОНИИ

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Comparison of Chest CT Findings between COVID-19 Pneumonia and Influenza Pneumonia

Резюме

Введение. С ростом мировой проблемы распространенности COVID-19 визуализация органов грудной клетки имеет важнейшее значение для эффективной постановки диагноза и лечения. Необходимо разграничивать характерные черты пневмонии, вызванной COVID-19, и других вирусных пневмоний, например, гриппа, на снимках. С этой целью проводилось исследование для сравнения результатов КТ грудной клетки при пневмонии, вызванной COVID-19, и гриппозной пневмонии. **Методы.** В период с марта по май 2020 г. в исследовании приняло участие 50 пациентов с симптомами со стороны органов дыхания и положительным результатом ПЦР (ПЦР-ОТ) в режиме реального времени мазков из носоглотки на грипп и 50 пациентов с симптомами со стороны органов дыхания и положительным результатом ПЦР в режиме реального времени мазков из носоглотки на COVID-19. В документацию пациентов заносили демографическую информацию (возраст, пол), результаты лабораторных исследований, включая С-реактивный белок, СОЭ, лейкоциты, а также клинические симптомы (повышение температуры, кашель, усталость, одышка). **Результаты.** Симптомы со стороны ЖКТ, отсутствие аппетита, высокий С-реактивный белок, симптом «матового стекла» чаще встречаются у пациентов с пневмонией, вызванной COVID-19, чем у пациентов с гриппозной пневмонией, поэтому это различие является статистически значимым (P <0,05). Тем не менее, повышение температуры чаще наблюдается при гриппозной пневмонии, чем при пневмонии, вызванной COVID-19, поэтому это различие является статистически значимым (P= 0,029). Что касается расположения поражений на снимках КТ, у пациентов с COVID-19 поражаются периферические участки (54 %), а у пациентов с гриппозной пневмонией — чаще центральные зоны (32 %), что является статистически значимым (P <0,05). **Заключение.** Согласно результатам исследования, снимки КТ органов грудной клетки вкупе с некоторыми клиническими и лабораторными показателями могут помочь разграничить

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пневмонию, вызванную COVID-19, и гриппозную пневмонию, что крайне важно для скорейшей постановки диагноза и своевременного лечения обоих заболеваний.

Ключевые слова: *компьютерная томография, COVID-19, грипп, рентгенография, заболевания легких, диагностическая визуализация*

Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Introduction: With increasing global concerns about the prevalence of COVID-19, chest imaging findings are essential for effective diseases diagnosis and treatment. There is a need to distinguish between imaging features of COVID-19 pneumonia and other viral pneumonia like Influenza.For this purpose, a study was performed on a comparison of chest CT findings between COVID-19 pneumonia and Influenza pneumonia. **Methods:** Fifty patients with respiratory symptoms and positive real-time PCR (RT-PCR) of nasopharyngeal swab for Influenza and fifty patients with respiratory symptoms and positive real-time PCR (RT-PCR) of nasopharyngeal swabfor COVID-19 from March to May 2020 were enrolled in the study. In the patient's checklist, information such as demographic characteristics (age, sex), laboratory findings including (CRP, ESR, WBC), and clinical signs (fever, cough, fatigue, dyspnea) were also recorded. **Results:** Gastrointestinal symptoms, anorexia, high CRP, ground-glass opacityare more common in patients with COVID-19 pneumonia than in patients with influenza pneumonia and this difference was statistically significant (P <0.05). But, fever is more common in influenza patients than in Covid-19 patients and this difference is statistically significant (P=0.029). The location of CT scan findings in COVID-19 patients was dominant in peripheral (54 %), while the location of CT scan findings in patients with Influenza was dominant in central (32 %), which is statistically significant (P <0.05). **Conclusion**: According to the results of the study, lung CTscan findings along with some clinical and laboratory findings can help differentiate COVID-19 pneumonia from influenza pneumonia, which is very important in faster diagnosis and timely treatment of both diseases.

Key words: *Computed tomography, COVID-19, Influenza, Radiology, Lung Diseases, Diagnostic Imaging*

Conflict of interests
The authors declare no conflict of interests

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COVID-19 — Corona virus disease of 2019, SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2, RT-PCR: real-time polymerase chain reaction, CRP — C-reactive protein, ESR — erythrocyte sedimentation rate, WBC — white blood cells, WHO — World Health Organization, ARS — Acute Respiratory Syndrome, CDC — centers for Disease control and Prevention, RNA — ribonucleic acid, H1N1 — hemagglutinin1 neuraminidase1, HRCT — high-resolution computed tomography, GGO — ground-glass opacity, DAD — diffuse alveolar damage

Introduction

In late 2019, the World Health Organization (WHO) warned of numerous cases of respiratory disease of unknown origin from Wuhan, China, with clinical presentations similar to those of viral pneumonia and patients often had pulmonary parenchymal opacity on chest radiography. Analysis of bronchoalveolar lavage fluid samples and electron microscopy showed that the cause of this disease was coronavirus. The newly discovered virus was temporarily named (coronavirus 2019, SARS-CoV-2). The main route of transmission of the virus is through respiratory droplets as well as physical contact [1, 2]. Before the current COVID-19 epidemic, there have been several global outbreaks of Acute Respiratory Syndrome (ARS). ARS is one of the leading causes of death and disease in the world, commonly caused by viruses including influenza, rhinovirus, enterovirus, coronavirus, respiratory syncytial virus, parainfluenza, and adenovirus. The most recent of ARS was the influenza A (H1N1) epidemic in 2009, which spread to 214 countries between March 2009 and August 2010, resulting in 18,449 deaths worldwide [3,

4]. The gold standard for diagnosing these viral infections is the confirmation of viral RNA by real-time reverse transcription-polymerase chain reaction (RT-PCR). However, according to a previous report on COVID-19, the positive rate of RT-PCR in the initial presentation is 30-60 %. This may be due to low viral load, hence the need for repeated tests [5]. Existing kits for testing for respiratory viruses are reported to have a sensitivity of 66-100 % [6]. However, in some cases, it may have a false-negative result, which may have been due to insufficient viral material in the sample or technical problems during nucleic acid extraction [7]. In such cases, with typical clinical manifestations, computed tomography (CT) may be a valuable asset and show disease even with a negative RT-PCR screening test [8]. According to the WHO and centers for Disease control and Prevention (CDC) Guidelines, chest radiographs and CT scans were the most important diagnostic devices at the time of the SARS outbreak [9]. Thus, CT of the chest, especially high-resolution computed tomography (HRCT), is a valuable tool in identifying patients in the early-stagesof respiratory infections like COVID-19 and Influenza. Other imaging techniques, such as plain chest radiographs, can help assess many chest disorders, including viral chest infections [8, 10]. With increasing global concerns about the prevalence of COVID-19, chest imaging findings are essential for effective diseases diagnosis and treatment. CT scan has higher resolution and more ability to prepare accurate chest anatomy than a plain chest radiographs and also it is a better tool to compare patients with Influenza and COVID-19. There is a need to distinguish between imaging features of COVID-19 pneumonia and other viral pneumonia due to the similarity in clinical symptoms as well as laboratory findings, to provide focused care in any situation [3]. For this purpose, this study was performed on a comparison of chest CT findings between COVID-19 pneumonia and Influenza pneumonia.

Materials and methods

Patients

This retrospective cross-sectional study was reviewed and approved by the Ethics Committee of Babol University of medical sciences. The present study has conducted at Ayatollah Rohani hospital in Babol, Iran.Fifty patients with respiratory symptoms and positive real-time PCR (RT-PCR) of nasopharyngeal swab for Influenza and fifty patients with respiratory symptoms and positive real-time PCR (RT-PCR) of nasopharyngeal swab for COVID-19 from March to May 2020 were enrolled in the study. In the patient`s checklist, information such as demographic characteristics (age, sex), laboratory findings including (CRP, ESR, WBC), and clinical signs (fever, cough, fatigue, dyspnea) were also recorded. Patients with history of lung surgery or lung cancer were excluded from the study.

CT image review

All CT images were reviewed by two radiologists with approximately 10 years of experience in chest CT interpretation and then final decisions were reached by consensus. Disagreements were resolved by a third radiologist. The CT findings included ground-glass opacity (GGO), consolidation, air bronchogram, reticulation, pleural effusion, pleural thickening, nodules, distribution, air space opacity, pleurisy, atelectasis, and emphysema.

Statistical Analysis

We used version 22.0 of SPSS software for the statistical analysis. The Mann-Whitney and chi-square test was used to compare the differences between the two groups for continuous variables. A p-valueless than 0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics

Fifty patients with COVID-19 (mean age, 63 years; 29 men and 21 women) and 50 patientswith Influenza (mean age, 59 years; 22 men and 28 women) were enrolled in the study. They were no significant differences in mean age between the two groups (P >0.05). Gastrointestinal symptoms, anorexia, high CRP, and lymphocytopenia are more common in patients with COVID-19 than in patients with Influenza and this difference was statistically significant (P <0.05). But, fever is more common in ILI patients than in COVID-19 patients and this difference is statistically significant (P=0.029) (Table1).

CT Findings

Comparisons of the CT characteristics COVID-19 and influenza are presented in Table 2. There was no significant difference between the two groups concerningnodules, pleural effusion, pleural thickening, air space opacity, air bronchogram, atelectasis, pleurisy, and emphysema (P >0.05). The following findings did reach statistical significance in COVID-19 and influenza group: GGO (43 vs 25, respectively; P=0.002), consolidation (22 vs 23 patients, respectively; P=0.01) and distribution (49 vs 26, respectively; P <0.0001).

Table 1. *Demographic and clinical characteristics in patients with COVID-19 and with influenza*

Parameters	Covid-19 (n=50)	Influenza (n=50)	P <0.05
Age	63.26 ± 20.64	59.62 ± 21.27	0.38
Sex:			
Male	29(58 %)	22 (44 %)	
Female	21 (42 %)	28 (56 %)	
Signs and symptoms:			
Fever	38(76 %)	46 (92 %)	0.029
Cough	41 (82 %)	33 (66 %)	0.06
Myalgia	29 (58 %)	32(64 %)	0.53
Dyspnea	37 (74 %)	28 (56 %)	0.059
Headache	14 (28 %)	17 (34 %)	0.51
Fatigue	32 (64 %)	26 (52 %)	0.22
Gastrointestinal symptoms	19 (38 %)	2 (4 %)	0.003
Anorexia	33 (66 %)	23 (46 %)	0.04
Laboratory assay results:			
Leukocytosis	14 (28 %)	7 (14 %)	0.94
Leukopenia	7 (14 %)	6 (12 %)	
ESR	27 (54 %)	26 (52 %)	0.84
CRP	39 (78 %)	24 (48 %)	0.0001
Lymphocytopenia	27 (54 %)	17 (34 %)	0.04
Neutrophilia	10 (20 %)	18 (36 %)	0.07

Таблица 2. *Результаты КТ 50 пациентов с COVID-19 и 50 пациентов с гриппоподобным заболеванием*
Table 2. *CT imaging findings in 50 patients with COVID-19 and 50 with influenza-like illness*

CT findings	COVID-19	nfluenza-like illness	P <0.05
Ground glass opacity	43 (86 %)	25 (50 %)	0.002
Consolidation	22 (44 %)	23 (46 %)	0.01
Pleural effusion	8 (16 %)	11 (22 %)	0.28
Air bronchogram	3 (6 %)	6 (12 %)	0.29
Pleural thickening	9 (18 %)	3 (6 %)	0.06
Nodules	11 (22 %)	7 (14 %)	
single nodule	2 (18.2 %)	5 (71.4 %)	0.051
two and more nodules	9 (81.8 %)	2 (28.6 %)	
Air space opacity	4 (8 %)	3 (6 %)	0.69
Pleurisy	4 (8 %)	3 (6 %)	0.69
Atelectasis	6 (12 %)	3 (6 %)	0.29
Emphysema	2 (4 %)	4 (8 %)	0.39
Distribution			
peripheral distribution	27 (54 %)	4 (8 %)	<0.0001
central distribution	14 (28 %)	16 (32 %)	
peripheral and central	8 (16 %)	6 (12 %)	

Discussion

Clinical evidence, laboratory parameters, biomedical and imaging findings in patients with COVID-19and Influenza have been evaluated in a few studies. In Influenza from the histological point of view, mucosal/submucosal mononuclear cell infiltration of the bronchial walls with multifocal desquamation of the epithelium occur and in later stage, organized DAD (diffuse alveolar damage), massive intra-alveolar edema with variable degrees of hemorrhage is seen which in the CT of the chest, they show themselves as ground-glass opacities, focal areas of consolidation, bronchial wall thickening and airspace nodules [11, 12]. In COVID-19, the histological examination reveals mainly septal lymphatic stasis, edema and exudative or proliferative phase of DAD with excessive epithelial leakage and also vascular

damage and thrombosis which on CT of the chest manifests itself in the form of GGO with thickened interlobular septa and crazy paving [13].

Faster and more accurate differentiation of COVID-19 virus from other viruses with Pulmonary involvementis very important. Therefore, this study compared the findings of high-resolution CT scans in patients with COVID-19 and influenza. We also evaluated laboratory finding and clinical signs in addition to CT scan findings in two groups of patients. The common chest CT findings of mild to moderate influenza pneumonia consist of diffuse or multifocal ground-glass opacities and small centrilobular nodules and in mild to moderate stage of COVID pneumonia GGO is also the earliest and predominant CT abnormality that usually located peripherally compared with influenza which is central and random locations. Crazy pattern and reticular changes are more common in COVID-19 and the presence of it indicates an advanced disease stage [14, 15]. Both COVID-19 and influenza patients in severe stage (mainly patients with DAD and ARDS) show diffuse ground glass pattern and air filled cystic changes and with HRCT findings of parenchymal or alveolar involvement, it is not possible to distinguish them [16].

The most important result of the present study was the differentiation between the percentages of CT scan findings of patients with COVID-19 and influenza. In other words, GGO was more prevalent in COVID-19 patients than influenza (43 vs 25, respectively), and also consolidation was 46 % in patients withinfluenza and 44 % in patients with COVID-19. In a variety of respiratory infections, evidence of chest involvement such as GGO, consolidation, is characterized through radiographic evaluation and CT scan [17]. Also, studies of COVID-19 showed the most common attenuation was a pattern of consolidation and GGO [18-22]. Therefore, the study of imaging manifestations of COVID-19 in the early stages and providing imaging for early detection of suspected cases can help reduce the complications of the disease and increase the chance of recovery [23]. The frequency of nodules on CT scans also differed between the two diseases. Nodules on CT scans of COVID-19 patients were more than patients with influenza (22 % to 14 %). Our results were in line with the results expressed by Gao et al. that showed the number of nodules is in COVID-19 patients is higher than Influenza [20]. Another notable finding is that the order of location of CT scan involvement in patients with COVID-19 is also different from patients withinfluenza. According to the location of CT scan distribution, it was found that the site of lung involvement in patients with COVID-19 pneumonia was mostlyin the periphery but lung involvement in patients with influenza was mostly seen in central parts. Different studies have reported the same statistics on the prevalence of lesion distribution [18, 19, 21, 24].

The similarity of clinical symptoms between COVID-19 and other viral pneumonia in many cases leads to delayed diagnosis, increaseddisease progressionand mortality. Evaluation and comparison of clinical symptoms in patients with COVID-19 and patients with influenza have also been one of the objectives of the present study. The results showed the symptoms like fever, cough, headache, myalgia and fatigue were manifested by both COVID-19 disease and influenza. Dai et al. showed fever and cough were the main symptoms of patients with COVID-19 and patients with lung pneumonia (41). The results of Yin et al.'s study showed that fever, cough, sputum, and shortness of breath were the main symptoms in both COVID-19 and influenza pneumonia, but cough and sputum were more common in the influenza group (48). In our study, there was a significant differencein the prevalence of dyspnea, gastrointestinal symptoms, and anorexia between two groups and these were more common in patients with COVID-19. So, maybe these symptoms can be used as one of the criteria for differentiating COVID-19 from influenza pneumonia. Examination of laboratory parameters showed the level of CRP as well as lymphopenia in patients with COVID-19was more than in patients with influenza. The result of the Yin et al. study is similar to our study (48).

Based on the results of our study, lung CTscan findings along with some clinical and laboratory findingscan help differentiate COVID-19 pneumonia from influenza pneumonia, which is very important in faster diagnosis and timely treatment of both diseases.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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ВЛИЯНИЕ ПОРАЖЕНИЯ ПОЧЕК НА ТЕЧЕНИЕ И ПРОГНОЗ ПРИ ИНФЕКЦИИ COVID-19 ПО ДАННЫМ МЕЖДУНАРОДНОГО РЕГИСТРА «АНАЛИЗ ДИНАМИКИ КОМОРБИДНЫХ ЗАБОЛЕВАНИЙ У ПАЦИЕНТОВ, ПЕРЕНЕСШИХ ИНФИЦИРОВАНИЕ SARS-COV-2»

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Impact of Kidney Damage on the Course and Prognosis of COVID-19 Infection According to the International Registry «Analysis of Chronic Non-Infectious Diseases Dynamics After Covid-19 Infection in Adult Patients»

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Резюме

Цель. Изучение особенностей течения новой коронавирусной инфекции (НКИ) у пациентов с хронической болезнью почек (ХБП), выявление случаев возникновения острого повреждения почек (ОПП) на фоне инфекции COVID-19 и влияние состояния функции почек на прогноз у таких категорий пациентов в острый и постгоспитальный периоды, спустя 3, 6 и 12 месяцев после выздоровления. **Материалы и методы**. В регистр АКТИВ и АКТИВ 2 были включены мужчины и женщины старше 18 лет с диагнозом COVID-19, выставленным на основании положительного ПЦР-теста на COVID-19 и данных характерной рентгенографической или компьютерно-томографической картины органов грудной клетки. **Результаты**. Всего в анализ было включено 9364 пациента (4404 мужчин, средний возраст 59 [48-69]), из них ХБП встречалась у 716 (7,67 %) пациентов, регистрация скорости клубочковой фильтрации (СКФ) во время госпитализации осуществлялась у 8496 (90,7 %) пациентов, значения были распределены следующим образом: ≥90 мл/мин/1,73м^2 — у 4289 (50,5 %) пациентов, 89-60 мл/мин/1,73м^2 — у 3150 (37,1 %) пациентов, 59-45 мл/мин/1,73м^2 — у 613 (7,22 %), 44-30 мл/мин/1,73м^2 — у 253 (2,98 %), 29-15 мл/мин/1,73м^2 — у 110 (1,29 %), <15 мл/мин/1,73м^2 — у 81 (0,95 %) пациента. В 11,6 % случаев (1068 пациентов) за время нахождения в стационаре развилось ОПП, это осложнение формировалось чаще, чем цитокиновый шторм (в 7,46 % у 687 пациентов, p<0,001) или сепсис (в 0,17 % у 16 пациентов, p=0,620). ХБП повышала риск смерти у пациентов с COVID-19 на госпитальном этапе в 3,94 раза в сравнении с пациентами без ХБП. У пациентов с ОПП летальный исход на госпитальном этапе был в 3,94 раза больше, чем у людей без ОПП. Наличие ХБП влияло на выживаемость и в отдалённом постгоспитальном периоде: в течение 3-х месяцев наблюдения риск смерти при наличии ХБП возрастал в 4,88 раза, в течение 6 месяцев — в 4,24 раза, через 12 месяцев — в 8,36 раза. **Заключение**. Распространенность ХБП в группе пациентов с COVID-19 равнозначна таковой в популяции в целом. ОПП развивалась в 11,6 % случаев при инфекции COVID-19 и чаще наблюдалась у пациентов с избыточным весом и гипергликемией. ХБП и ОПП повышали риск госпитальной летальности у пациентов с COVID-19. В постковидном периоде на протяжении 3, 6 и 12 месяцев после выздоровления отмечалось повышение смертности в группе пациентов с ХБП. У пациентов, перенесших ОПП в период коронавирусной инфекции, высокая смертность в постковидном периоде отмечалась только в первые 3 месяца наблюдения.

Ключевые слова: *COVID-19, хроническая болезнь почек, острое повреждение почек*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Objective. To study the course of the new coronavirus infection in patients with chronic kidney disease (CKD), to identify cases of acute kidney injury (AKI) in the setting of COVID-19 infection, and to access the impact of renal function on prognosis in these categories of patients during the acute phase and after hospitalization, at 3, 6, and 12 months after recovery. **Materials and methods.** The ACTIV and ACTIV 2 registries included men and women older than 18 years with a diagnosis of COVID-19 based on a positive PCR test for COVID-19 and a characteristic chest X-ray or computed tomography chest scan. **Results.** A total of 9364 patients (4404 men, average age59 [48-69]) were included in the analysis. 716 (7.67 %) patients had CKD. 8496 (90,7 %) patients had their glomerular filtration rate (GFR) measured during hospitalization, and the values were distributed as follows: ≥90 ml/min/1.73m^2 — in 4289 (50,5 %) patients, 89-60 ml/min/1.73m^2 — in 3150 (37,1 %) patients, 59-45 ml/min/1.73m^2 — in 613 (7,22 %), 44-30 ml/min/1.73m^2 — in 253 (2,98 %), 29-15 ml/min/1.73m^2 — in 110 (1,29 %), <15 ml/min/1.73m^2 — in 81 (0,95 %) patients. 11.6 % of the subjects (n=1068) developed AKI during hospitalization. This complication was reported more often than cytokine storm (in 7.46 % in 687 patients, p<0,001) or sepsis (in 0.17 % in 16 patients, p=620). CKD increased the risk of death by 3.94-fold in patients with COVID-19 during hospitalization compared with patients without CKD. The mortality of patients with AKI during hospitalization was 3.94 times higher than the mortality of those without AKI. CKD also affected long-term survival after hospitalization: within 3 months of follow-up, the risk of death in patients with CKD increased 4.88-fold, within 6 months — 4.24-fold, after 12 months — 8.36-fold. **Conclusion.** The prevalence of CKD in COVID-19 patients is similar to that in the general population. AKI developed in 11.6 % of cases with COVID-19 infection and was observed more frequently in patients with overweight and hyperglycemia. CKD and AKI increased the risk of hospital mortality in patients with COVID-19. In the group of patients with CKD, mortality increased in the post-COVID period, 3, 6 and 12 months after. The high mortality rate of patients who had AKI during the coronavirus infection was observed only in the first 3 months of follow-up in the post-COVID period.

Key words: *COVID-19, chronic kidney disease, acute kidney damage*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, ARB II — angiotensin II receptor blocker, BA — bronchial asthma, BB -beta-blocker, CCB — calcium channel-blocking agent, GC — glucocorticosteroid, ACE inhibitors — angiotensin converting enzyme inhibitors, IHD — ischemic heart disease, BMI — body mass index, CRF — case report form, CT — computer tomography, nCoV — novel coronavirus infection, NSAID — nonsteroidal anti-inflammatory drug, ACE — acute cerebrovascular event, AKI — acute kidney injury, OR — odd ratio, DM — diabetes mellitus, GFR — glomerular filtration rate, AHG — antihyperglycemic drug, AF — atrial fibrillation, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, CHF — chronic heart failure, RR — respiratory rate

Introduction

Management of patients with chronic kidney disease (CKD) and acute kidney injury (AKI) during coronavirus infection and post-COVID rehabilitation is a burning issue of the contemporary therapeutics and is widely discussed by Eurasian and national medical communities [1-4]. On the one hand, it is caused by the features of coronavirus infection in patients with impaired renal function and, on the other hand, by the need in medical support of this patient category, which can be associated with the need in renal replacement therapy [5, 6].

The need in information related to the features of coronavirus infection, in particular in patients with impaired renal function, was satisfied with the help of the following registers: Dynamics Analysis of Comorbidities in SARS-CoV-2 Survivors (AKTIV) and Analysis of Hospitalizations of Comorbid Patients with SARS-CoV-2 (AKTIV 2) [7-9].

Materials and Methods

The AKTIV and AKTIV 2 registers were initiated by the Eurasian Association of Therapists (EAT). The AKTIV and AKTIV 2 registers were approved by the Ethics Committee at the Federal State Autonomous Educational Institution of Higher Education N. I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation and registered in ClinicalTrials.gov (NCT 04492384, NCT 04709120). For information on the registers, please refer to the web site of the Eurasian Association of Therapists, or go to https://activ.euat.ru and https://activ2.euat.ru. AKTIV and AKTIV 2 registers are multicenter non-interventional retrospective registers of real-life clinical experience. AKTIV had two non-overlapping threads (outpatient thread and inpatient thread). Both threads provided for 6 visits: baseline visit, Day 7–12 visit, final visit (dismissal/hospitalization/death, etc.), and three visits — 3, 6, and 12 months after discharge from the hospital. AKTIV 2 register included information on hospitalised patients only and provided for 3 visits: baseline visit, Day 7–12 visit, final visit (dismissal/hospitalization/death, etc.).

Both registers included men and women over 18 years old with COVID-19 confirmed with a nasopharynx and oropharynx swab, SARS-CoV-2 antibody titer and/or typical computer tomography (CT) findings during the first (for AKTIV) and second (for AKTIV 2) coronavirus waves.

A primary document was the clinical record, which was used to fill out case report forms (CRF) with the following laboratory parameters: RBC, Hb, WBC, lymphocytes, platelets, highly sensitive cardiac troponin T or I, C-reactive protein, procalcitonin, arterial blood gases (pCO_2, pO_2), aspartate aminotransferase, alanine aminotransferase, bilirubin, glucose, albumin, creatinine for eGFR calculation, serum potassium, D-dimer, lactate dehydrogenase, international normalised ratio, fibrinogen, blood oxygen (SpO_2)), chest CT findings, information on drugs, comorbidities, clinical progression, and disease outcome. Glomerular filtration rate was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (Chronic Kidney Disease Epidemiology Collaboration Formula, CKD-EPI, version 2009, taking into account the time of active enrollment and register data processing) integrated with the automated calculator function in case report forms.

A nosologic diagnosis was made on the basis of ICD 10 criteria. More specifically, taking into account the register design, CKD was diagnosed with GFR of no less than 60 mL/min/1.73 m^2

The database was analysed using IBM SPSS Statistics 26. Continuous sampling method was used to select 9364 patients from AKTIV and AKTIV 2. For descriptive statistics calculations, quantitative variables were checked for normal distribution with the help of Shapiro-Wilk's test and Kolmogorov-Smirnov test. If the difference from normal distribution was not statistically significant, the central trend and measure of scatter were described using a mean sample value and standard deviation (M±σ); where the difference from normal distribution was statistically significant, the median and quartiles (Me [Q1; Q3]) were used. Quantitative data from two independent groups were analysed using Mann-Whitney test for independent samples with non-normal distribution (a normality test showed a distribution that was different from normal distribution); quantitative data from three and more groups were analysed with the help of Kruskall-Wallis test with subsequent pair-wise comparison. Qualitative parameters were evaluated using Pearson's chi-squared test or Fisher's exact test, depending on the expected minimal value. For features with statistically significant differences (level of significance < 0.05),

odds and certain relations between nominal characteristics were evaluated with 95 % CI.

Odds ratio (OR) and its 95 % CI were calculated using a one-factor binary logit regression method. The stage 1 mathematical model was generated using a multi-factor binary logit regression method, with variables selected by the authors taking into account study objectives and tasks. For the final model used to select the most significant estimate predictors, a stepwise downward variable selectin algorithm was implemented,

Table 1. *Characteristics of patients included in the АКТИВ and АКТИВ 2 registries with different baseline GFR values*

Characteristic	Total cohort n=9364	GFR ≥90 (n=4289)	GFR 89-60 (n=3150)	GFR 59-45 (n=613)	GFR 44-30 (n=253)	GFR 29-15 (n=110)	GFR <15 (n=81)	p
Age	59,0 [48,0; 68,0]	55,0 (43,0–63,0)	66,0 (57,0–73,0)	73,0 (66,0–81,0)	74,0 (66,0–83,0)	72,0 (61,0–81,0)	62,5 (54,5–71,0)	<0,001* $p_{1\,5}$<0,001* $p_{1\,2}$<0,001* $p_{1\,4}$<0,001* $p_{1\,3А}$<0,001* $p_{1\,3Б}$<0,001* $p_{5\,2}$=1,0 $p_{5\,4}$=0,007* $p_{5\,3А}$<0,001* $p_{5\,3Б}$<0,001* $p_{2\,4}$=0,019* $p_{2\,3А}$<0,001* $p_{2\,3Б}$<0,001* $p_{4\,3А}$=0,302 $p_{4\,3Б}$=0,295 $p_{3А\,3Б}$=1,0
Women	4960 (53 %)	1995 (46,5 %)	1799 (57,4 %)	388 (64,2 %)	1613 (64,7 %)	61 (55,5 %)	49 (61,3 %)	<0,001*
Lethal outcomes	545 (5,8 %)	100 (2,4 %)	184 (5,9 %)	86 (14,6 %)	80 (32,1 %)	42 (40,0 %)	15 (19,5 %)	<0,001*
Overweight	2934 (37,7 %)	1383 (37,9 %)	994 (38,0 %)	174 (35,1 %)	62 (30,4 %)	34 (37,4 %)	29 (39,7 %)	<0,001*
Obesity, degree 1	1701 (21,8 %)	771 %)	642 (24,5 %)	123 (24,8 %)	53 (26,0 %)	16 (17,6 %)	11 (15,1 %)	
Obesity, degree 2	669 (8,5 %)	311 (8,5 %)	248 (9,5 %)	42 (8,5 %)	25 (12,3 %)	12 (13,2 %)	4 (5,5 %)	
Obesity, degree 3	240 (3,08 %)	133 (3,6 %)	96 (3,7 %)	38 (7,7 %)	13 (6,4 %)	5 (5,5 %)	3 (4,1 %)	
CT 1	3136 (41,9 %)	1565 (44,2 %)	1126 (41,8 %)	167 (34,2 %)	64 (30,3 %)	20 (21,7 %)	25 (37,9 %)	<0,001*
CT 2	2563 (34,2 %)	1170 (33,1 %)	973 (36,1 %)	178 (36,5 %)	79 (37,4 %)	35 (38,0 %)	21 (31,8 %)	
CT 3	1005 (13,4 %)	455 (12,9 %)	363 (13,5 %)	87 (17,8 %)	42 (19,9 %)	16 (17,4 %)	12 (18,2 %)	
CT 4	231 (3,1 %)	92 (2,6 %)	73 (2,7 %)	25 (5,1 %)	13 (6,2 %)	13 (14,1 %)	3 (4,5 %)	
SpO_2 75-94 %	2166 (23,1 %)	856 (31,1 %)	810 (38,6 %)	209 (49,4 %)	94 (55,0 %)	42 (54,5 %)	21 (41,2 %)	<0,001*
SpO_2 less than 75 %	55 (0,6 %)	15 (0,5 %)	20 (1,0 %)	9 (2,1 %)	1 (0,6 %)	6 (7,8 %)	0	
Breathing rate 22-29	2314 (25,0 %)	1038 (24,3 %)	810 (25,9 %)	201 (33,5 %)	97 (39,0 %)	42 (38,5 %)	18 (22,5 %)	<0,001*
Breathing rate more than 30	178 (1,9 %)	52 (1,2 %)	66 (2,1 %)	25 (4,2 %)	14 (5,6 %)	9 (8,3 %)	4 (5,0 %)	
Temperature over 38.6-39.0	1634 (17,7 %)	780 (18,4 %)	583 (18,8 %)	115 (19,3 %)	48 (19,2 %)	20 (18,5 %)	11 (14,1 %)	<0,001*
Temperature over 39.0	640 (6,9 %)	354 (8,3 %)	210 (6,8 %)	36 (6,0 %)	11 (4,4 %)	7 (6,5 %)	4 (5,1 %)	
Hypertension	5289 (56,6 %)	1929 (45,1 %)	2196 (70,1 %)	506 (83,8 %)	211 (83,7 %)	85 (77,3 %)	62 (77,5 %)	<0,001*
Smoking	475 (5,09 %)	245 (5,7 %)	123 (3,9 %)	17 (2,8 %)	7 (2,8 %)	4 (3,6 %)	8 (10,8 %)	<0,001*
AF	672 (7,2 %)	157 (3,7 %)	284 (9,1 %)	113 (18,7 %)	65 (25,8 %)	23 (20,9 %)	6 (7,5 %)	<0,001*
IHD	2144 (23 %)	534 (12,5 %)	938 (29,9 %)	289 (47,8 %)	127 (50,4 %)	51 (46,4 %)	26 (32,5 %)	<0,001*
CHF	1595 (17,1 %)	413 (9,7 %)	685 (21,9 %)	241 (39,9 %)	111 (44,0 %)	52 (47,3 %)	24 (30,0 %)	<0,001*
CVA	401 (4,29 %)	95 (2,2 %)	183 (5,8 %)	49 (8,1 %)	35 (13,9 %)	13 (11,8 %)	6 (7,5 %)	<0,001*
DM type 2	1611 (17,3 %)	592 (13,8 %)	602 (19,2 %)	191 (31,6 %)	86 (34,1 %)	32 (29,1 %)	21 (26,3 %)	<0,001*
COPD	408 (4,3 %)	151 (3,5 %)	150 (4,8 %)	44 (7,3 %)	28 (11,1 %)	7 (6,4 %)	8 (10,0 %)	<0,001*
BA	321 (3,44 %)	138 (3,2 %)	122 (3,9 %)	23 (3,8 %)	6 (2,4 %)	2 (1,8 %)	3 (3,8 %)	0,487
Cancer	536 (5,74 %)	195 (4,6 %)	212 (6,8 %)	48 (7,9 %)	25 (9,9 %)	12 (10,9 %)	5 (6,3 %)	<0,001*
Anemia	1976 (22,7 %)	809 (19,3 %)	636 (20,8 %)	188 (31,9 %)	110 (44,7 %)	61 (56,0 %)	56 (70,0 %)	<0,001*

Note: BA — bronchial asthma, IHD — ischemic heart disease, CT — computed tomography, CVA — acute cerebrovascular accident, DM — diabetes mellitus, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CHF — chronic heart failure;
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis.

which was followed by AIC (Akaike information criterion) evaluation. Once the final model had been generated using the ROC analysis, the area under curve (AUC) was evaluated, while the model sensitivity and specificity were evaluated in Youden point. The survival time was analysed using Kaplan-Meier's survival curves; statistical significance of the differences in evaluation of the survival time was evaluated using the log-rank test. The cuttoff threshold for the level of significance in statistical hypotheses testing was $p < 0.05$. Predictors with the level of significance of $p \geq 0.05$ could be used in the final model, provided that their exclusion would result in a marked increase in AIC (features interaction effect). The design, justification and statistical analysis of the studies are detailed in the article [10].

All in all, 9364 patients were included in the analysis (4404 (47 %) men, mean age: 59 years old [48–69]). Glomerular filtration rate (GFR) upon admission which was calculated automatically when blood plasma creatinine was entered upon admission on day 1, was recorded in 8496 (90.7 %) patients, with the following distribution of results: ≥ 90 mL/min/1.73 m^2 — 4289 (50.5 %) patients; 89–60 mL/min/1.73 m^2 — 3150 (37.1 %) patients, 59–45 mL/min/1.73 m^2 — 613 (7.22 %) patients, 44–30 mL/min/1.73 m^2 — 253 (2.98 %) patients, 29–15 mL/min/1.73 m^2 — 110 (1.29 %) patients, < 15 mL/min/1.73 m^2 — 81 (0.95 %) patients.

Mean age of patients which were added to the register was 59.0 years old [48.0; 68.0]. The maximum age was observed in the cohort with GFR of 44–30 mL/min/1.73 m^2 — 74.0 years old [66.0–83.0], the minimal age — in patients with GFR of over 90 mL/min/1.73 m^2 — 55.0 years old [43.0–63.0]. 4960 (53 %) patients were females. In the groups with various GFR values, the distribution of deaths was as follows: GFR of over 90 mL/min/1.73 m^2 — 100 (19.7 %) patients, 89–60 mL/min/1.73 m^2 — 184 (36.3 %) patients, 59–45 mL/min/1.73 m^2 — 86 (16.8 %) patients, 44–30 mL/min/1.73 m^2 — 80 (15.8 %) patients, 29–15 mL/min/1.73 m^2 — 42 (8.3 %) patients, GFR of less that 15 mL/min/1.73 m^2 — 15 (2.8 %) patients; p overall < 0.001.

Patients with GFR of 59–15 mL/min/1.73 m^2 vs. patients with GFR of over 60 mL/min/1.73 m^2 tended to more frequently have severe changes in their lungs (CT 3–4, p <0.001), impaired saturation (75–94 % and below 75 %, p <0.001), increased RR (over 22 respirations per minute, p <0.001), fever (over 38.6°C).

Both the general cohort and patients with GFR below 60 mL/min/1.73 m^2 had the following most common comorbidities: arterial hypertension (AH) (p <0.001), ischemic heart disease (IHD) (p <0.001), chronic heart failure (CHF) (p < 0.001), anemia (p <0.001), type 2 diabetes mellitus (DM2) (p <0.001).

ANALYSIS RESULTS

Incidence of Renal Diseases (CKD, AKI) in Patients with COVID-19

It should be noted that the AKTIV register included 716 (7.67 %) SARS-CoV-2 patients with pre-existing CKD; this number corresponds to the information on CKD incidence in the general population in the Russian Federation [11]. A proportion of CKD patients was higher in the group of patients over 60 years old (11.9 % of patients over 60 years old) and lower in patients below 60 years old (3.53 % of the total number of patients below 60 years old). CKD distribution taking into account GFR in the groups of patients below 60 years old and over 60 years old was not calculated.

CKD with AH, DM2 and obesity increased the need in anti-cytokine therapy in COVID-19 patients, and this is an indirect reason for more severe course of coronavirus infection in patients with CKD (Table 2).

According to Table 2, COVID-19 patients who did not require targeted therapy included patients with CKD; however, the group of patients who required anti-cytokine therapy included a significant number of patients with CKD. Apparently, CKD comorbidities have a role to play. A more severe infection was recorded in patients with CKD and comorbidities, rather than in CKD alone. This trend was observed also in evaluation of odds ratio (OR): OR was indeed higher in patients with CKD.

AKI symptoms were recorded in 9206 (98.3 %) questionnaires. During hospitalisation, AKI developed in 11.6 % (1068 patients out of 9206 patients), i.e., in every 8–9th patient. When the AKI data from the register were analysed, either physician's notes from medical records or the difference in creatinine levels of ≥ 30 μmol/L [12] during hospitalisation, which were measured twice, were taken into account. It is worth mentioning that AKI developed more frequently than cytokine storm (7.46 %, 687 patients out of 9209 patients) or sepsis (0.17 %, 16 patients out of 9411 patients) (p < 0.001). In identified AKI cases, changes in creatinine levels corresponded to stage 1 (because of the study design, diuresis was not assessed).

When analysing the register database, the authors attempted to single out risk factors affecting development of AKI and a number of other complications in patients with COVID-19. After a follow-up examination (assessment of creatinine level changes, CRP, CT stage, previous target therapy), the sample group was divided into two groups depending on the presence or absence of the following signs: AKI, cytokine storm, C-reactive protein (CRP) level of over 100 mg/L. Then, the body mass index (BMI) was assessed for each group (Table 3).

Mean BMI values for patients with or without AKI corresponded to overweight. BMI in patients with AKI was statistically higher than the BMI of patients without AKI (p = 0.018). In the AKI group, BMI was 29.6 mg/m^2

Table 2. *Comparison of study groups of patients with COVID-19 according to the frequency of targeted therapy depending on the comorbidities*

Factor	Did not receive targeted therapy	Received targeted therapy	p	V	OR; 95 % CI
		Hypertension			
	n=9047	n=292			
No	3951 (43,7 %)	99 (33,9 %)	0,001	0,034	1,51; 1,18–1,93
Yes	5096 (56,7 %)	193 (66,1 %)			
		DM type 2			
	n=9047	n=292			
No	7525 (83,2 %)	203 (65,9 %)	<0,001	0,063	2,17; 1,68–2,80
Yes	1522 (16,8 %)	89 (30,5 %)			
		CKD			
	n=9047	n=292			
No	8377 (92,6 %)	246 (84,2 %)	<0,001	0,055	2,34; 1,69–3,23
Yes	670 (7,4 %)	46 (15,8 %)			
		Obesity			
	n=8990	n=291			
No	6645 (73,9 %)	186 (63,9 %)	<0,001	0,040	1,6; 1,25–2,04
Yes	2345 (26,1 %)	105 (36,1 %)			

Note: DM — diabetes mellitus, CKD — chronic kidney disease.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis. Only 9281 (99,1 %) patient questionnaires our of 9364 contained information on the use or non-use of targeted therapy together with the obesity status. The targeted therapy was defined as Salirumab, Olokizumab and Levilimab.

Table 3. *The influence of BMI on various factors (Mann-Whitney test)*

Characteristic	Characteristic absent Me (Q1 — Q3)	Characteristic present Me (Q1 — Q3)	p
AKI	27,8 (24,8–31,6)	29,6 (25,1–33,5)	0,018
Cytokine storm	27,5 (24,4–31,2)	28,7 (25,6–32,8)	<0,001
CRP level more than 100 мг/л	27,7 (24,7–31,7)	28,7 (25,5–32,7)	<0,001
Mortality rate	5,7 (5,0–7,0)	6,9 (5,6–9,18)	<0,001

Note: BMI — body mass index, AKI — acute kidney injury, CRP — C-reactive protein

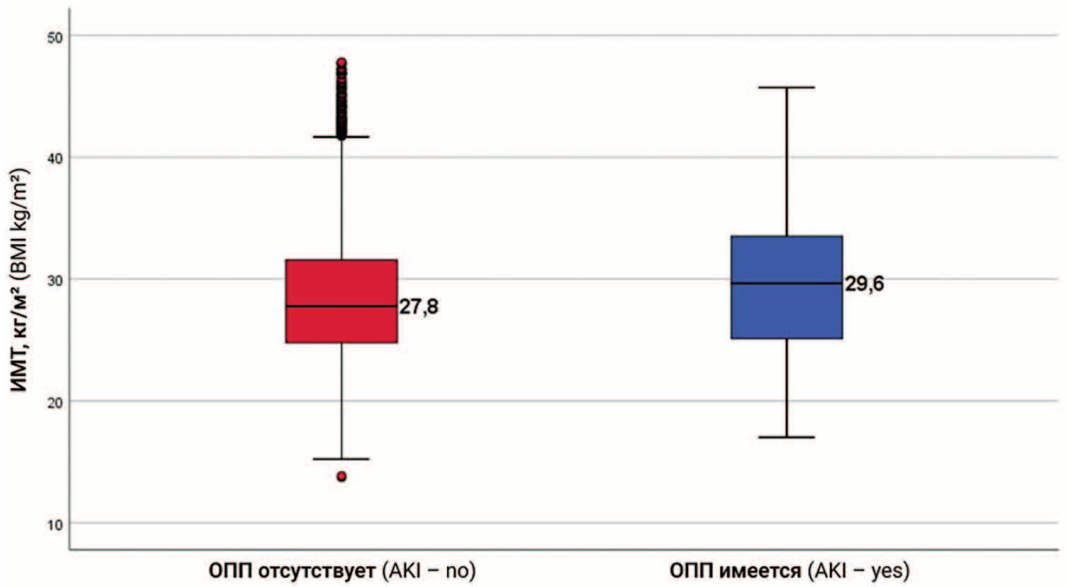

Figure 1. *Relationship between the presence and absence of AKI and BMI*
Note: BMI — body mass index, AKI — acute kidney injury

(Q1 = 25.1; Q3 = 33.5), whereas patients without AKI had BMI of 27.8 kg/m^2 (Q1 = 24.8; Q3 = 31.6) (Figure 1).

Fasting glucose levels were assessed. In patients with coronavirus infection and AKI, the values were 6.0 (5.2; 8.55) mmol/L, i.e., statistically higher than in patients without AKI (5.8 (5.0; 7.0) mmol/L) (p = 0.011).

Analysis of CKD and AKI Impact on Hospital Mortality and Post-Covid Mortality

Analysis of hospital mortality depending on the presence or absence of CKD is presented in Table 4. It was observed that CKD increased the risk of death in COVID-19 patients by 3.94 times (95 % CI [3.15; 4.89], 0.0001); therefore, CKD can be a factor of adverse hospital outcome in COVID-19 patients. At the same time, the risk of hospital mortality in the presence of CKD was higher in the group of patients below 60 years old (OR = 5.0, CI [2.59; 8.91], p < 0.001) vs. patients over 60 years old (OR = 2.61 CI [2.05; 3.30], p < 0.001).

The risk of hospital mortality was extremely high in the group of patients with GFR of 44–30 mL/min/1.73 m^2 (OR = 19.5, CI [14.0; 27.2]) and 29–15 mL/min/1.73 m^2 (OR = 27.6, CI [17.7; 42.7]), corresponding to CKD stages 3B and 4 with subsequent minor reduction in the risk at CKD stage 5. It is worth mentioning that there were just 78 (0.9 %) stage 5 patients, including 62 (79.5 %) patients who survived and 16 (20.5 %) patients who died, which could potentially affect statistics. According to observations of CKD stage 5 patients (n = 72,734) in Russia, mortality in COVID-19 patients is high (approx. 24.4 %) [13].

The odds of dying during hospitalisation in COVID-19 patients who develop AKI is 3.94 times higher than in patients without AKI (CI [3.24; 4.78], p = 0.0001).

The register database analysis demonstrated that CKD in patients with coronavirus infection also increases the risk of death during the post-COVID period (Table 5). During the first three months of the follow-up period, the risk of death in patients with CKD increased 4.88-fold (CI [2.42; 9.13], p < 0.001); during the six months of the follow-up period, there was a 4.24-fold increase (CI [0.60; 16.3], p = 0.126); and in 12 months the risk increased 8.36-fold (CI [1.73; 29.3], p = 0.012). Thus, even in a distant prospect of a year-long follow-up, when the mortality during the post-COVID period in the general population falls, the impact from CKD on survival rates was even higher.

It is essential to understand whether AKI during COVID affects mortality rates during the post-COVID period (Table 6). The analysis demonstrated that this impact was observed during the first three months only. At the same time, the odds of dying in 3 months after COVID for patients who had AKI during thier disease was 3.59 tims higher vs. patients without AKI (CI [1.87; 6.50], p < 0.001). AKI management during coronavirus infection was associated with high mortality rates over a short period of time (for three months) with gradual evening out (Table 6).

Table 4. *Comparison of the impact of renal factors on in-hospital mortality in patients with COVID-19*

	Survivors N=8662	Lethal outcomes N=545	OR; 95 % CI	p. ratio	p-overall	Total number
CKD — no	8067 (93,3 %)	425 (78,0 %)				
CKD — yes	579 (6,70 %)	120 (22,0 %)	3,94 [3,15; 4,89]	0,0001		
CKD up to 60 years old — no	4428 (96,7 %)	77 (85,6 %)			<0,001	4669
CKD up to 60 years old — yes	151 (3,30 %)	13 (14,4 %)	5,00 [2,59; 8,91]	<0,001		
CKD over 60 years — no	3612 (89,5 %)	348 (76,5 %)			<0,001	4493
CKD over 60 years — yes	426 (10,5 %)	107 (23,5 %)	2,61 [2,05; 3,30]	<0,001		
GFR						8388
≥ 90 ml/min/1.73m^2	4147 (52,6 %)	100 (19,6 %)				
89-60 ml/min/1.73m^2	2926 (37,1 %)	185 (36,3 %)	2,62 [2,05; 3,37]	<0,001		
59-45 ml/min/1.73m^2	511 (6,49 %)	86 (16,9 %)	6,98 [5,15; 9,44]	0,0001		
44-30 ml/min/1.73m^2	170 (2,16 %)	80 (15,7 %)	19,5 [14,0; 27,2]	0,0001		
29-15 ml/min/1.73m^2	63 (0,80 %)	42 (8,25 %)	27,6 [17,7; 42,7]	0,0001		
<15 ml/min/1.73m^2	62 (0,79 %)	16 (3,14 %)	10,8 [5,80; 18,9]	<0,001		
AKI					<0,001	9207
AKI no	7769 (89,7 %)	375 (68,8 %)				
AKI yes	893 (10,3 %)	170 (31,2 %)	3,94 [3,24; 4,78]	0,0001		

Note: AKI = acute kidney injury, GFR = glomerular filtration rate, CKD = chronic kidney disease
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Table 5. *Analysis of mortality in the post-COVID period depending on CKD at baseline*

Visit		CKD no	CKD yes
Visit 4 (3 months after the discharge)	Survived N=3089	2931 (94,9 %)	158 (5,11 %)
	Died N=58	46 (79,3 %)	12 (20,7 %)
	OR, 95 %CI	Ref.	4,88 [2,42; 9,13]
	p-ratio	Ref.	<0,001
	p overall	<0,001	
Visit 5 (6 months after the discharge)	Survived N=2485	2377 (95,7 %)	108 (4,35 %)
	Died N=13	11 (84,6 %)	2 (15,4 %)
	OR, 95 %CI	Ref.	4,24 [0,60; 16,3]
	p-ratio	Ref.	0,126
	p overall	0,109	
Visit 6 (12 months after the discharge)	Survived N=1774	1704 (96,1 %)	70 (3,95 %)
	Died N=12	9 (75,0 %)	3 (25,0 %)
	OR, 95 %CI	Ref.	8,36 [1,73; 29,3]
	p-ratio	Ref.	0,012
	p overall	0,011	

Note: CKD stands for chronic kidney disease.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Table 6. *Analysis of long-term mortality in patients with COVID-19, depending on the presence/absence of AK*

Visit		AKI no	AKI yes
Visit 4 (3 months after the discharge)	Survived N=3103	2849 (91,8 %)	254 (8,19 %)
	Died N=58	44 (75,9 %)	14 (24,1 %)
	OR, 95 %CI	Ref.	3,59 [1,87; 6,50]
	p-ratio	Ref.	<0,001
	p overall	<0,001	
Visit 5 (6 months after the discharge)	Survived N=2493	2294 (92,0 %)	199 (7,98 %)
	Died N=13	11 (84,6 %)	2 (15,4 %)
	OR, 95 %CI	Ref.	2,22 [0,31; 8,50]
	p-ratio	Ref.	0,360
	p overall	0,280	
Visit 6 (12 months after the discharge)	Survived N=1782	1649 (92,5 %)	133 (7,46 %)
	Died N=12	12 (100,0 %)	0 (0,0 %)
	OR, 95 %CI	Ref.	8,36 [1,73; 29,3]
	p-ratio	Ref.	0,99
	p overall	1,00	

Note: AKI stands for acute kidney injury.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Impact from the Drug Therapy on Mortality Rates in COVID-19 Patients with CKD

It can be interesting to review the data on the impact from various drug therapies on survival rates in COVID-19 patients with CKD (Table 7). The total number of CKD patients was 693, including 120 patients who died (17.3 %) and 573 survivors (82.7 %).

The use of ARB was associated with a decrease in mortality rates in patients with CKD during the infection (OR 0.5, CI [0.3; 0.8], p = 0.004). In patients who died, ARB was administered in 15.8 % of cases (19 patients), while in the survivor group it was administered in 28.4 % of cases (163 patients). There was just an insignificant association between compared parameters (V = 0.047). The odds of death in patients with CKD who were treated with hydroxychloroquine decreased 1.7-fold (95 % CI: 0.4–0.99). There was just an insignificant association between compared parameters (V = 0.077).

At the same time, ACE inhibitors did not have any significant impact over the risk of death (p > 0.05). Statin, BB, and CCB therapy did not have any significant impact on the survival rates in CKD patients (p > 0.05). The use of therapies for making COVID-19 less severe (inhalation or IV steroids, paracetamol, acetylsalicylic acid, antihistamines, bronchodilators, and targeted therapy did not have any impact on mortality rates in patients with CKD (p > 0.05). Nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with a minor, but statistically significant decrease in mortality rates. The odds of dying in patients with CKD who took NSAIDs was 2 times lower (95 % CI: 0.3–0.9, p = 0.030). There was just an insignificant association between compared parameters (V = 0.082). The odds of dying in patients with CKD who took antihyperglycemic (AHG) tablets decreased by 3.3 times (95 % CI: 0.1–0.8, p = 0.011). There was just an insignificant association between compared parameters (V = 0.097).

The use of hydroxychloroquine had a positive effect on survival rates (OR 0.6, CI [0.4; 0.99], p = 0.043. There was just an insignificant association between compared parameters (V = 0.077). The odds of dying in patients with CKD who were treated with interferons increased by 4.2 times (95 % CI: 1.5–11.6, p = 0.007). There was just a minor association between compared parameters (V = 0.142). The odds of dying in patients with CKD who were treated with diuretics increased by 1.7 times (95 % CI: 1.2–2.6, p = 0.007). There was just a minor association between compared parameters (V = 0.102). The odds of death in patients with CKD who were treated with expectorant drugs decreased by 0.6 times (95 % CI: 0.4–0.9, p = 0.009). There was just a minor association between compared parameters (V = 0.1).

Since there were no deaths in patients with AKI in treatment groups, the AKI impact on mortality rates could not be assessed.

Table 7. *Survival of patients with CKD and COVID-19 infection according to the therapeutic intervention*

Class of drugs	Survivors (n=573)	Lethal outcomes (n=120)	p	OR; 95 %CI	Cramer's V
ACE inhibitors					
Not prescribed	373 (65,1 %)	71 (59,2 %)	0,218		0,047
Prescribed	200 (34,9 %)	49 (40,8 %)			
ARA					
Not prescribed	410 (71,6 %)	101 (84,2 %)	0,004*	0,5 (0,3–0,8)	0,108
Prescribed	163 (28,4 %)	19 (15,8 %)			
Statins					
Not prescribed	423 (73,8 %)	84 (70,0 %)	0,390		0,033
Prescribed	150 (26,2 %)	36 (30,0 %)			
BB					
Not prescribed	297 (51,8 %)	66 (55,0 %)	0,528		0,024
Prescribed	276 (48,2 %)	54 (45,0 %)			
CCB					
Not prescribed	428 (74,7 %)	94 (78,3 %)	0,401		0,032
Prescribed	145 (25,3 %)	26 (21,7 %)			
ICS					
Not prescribed	562 (98,1 %)	116 (96,7 %)	0,308		0,037
Prescribed	11 (1,9 %)	4 (3,3 %)			

Таблица 7. *(Окончание)*
Table 7. *(The end)*

Class of drugs	Survivors (n=573)	Lethal outcomes (n=120)	p	OR; 95 %CI	Cramer's V
		Paracetamol			
Not prescribed	320 (55,8 %)	75 (62,5 %)	0,181		0,051
Prescribed	253 (44,2 %)	45 (37,5 %)			
		Aspirin			
Not prescribed	451 (78,7 %)	96 (80,0 %)	0,752		0,012
Prescribed	122 (21,3 %)	24 (20,0 %)			
		NSAIDs			
Not prescribed	475 (82,9 %)	109 (90,8 %)	0,030*	0,5 (0,3–0,9)	0,082
Prescribed	98 (17,1 %)	11 (9,2 %)			
		Antihistamines			
Not prescribed	355 (97,8 %)	92 (100 %)	0,368		0,067
Prescribed	8 (2,2 %)	0			
		Bronchodilators			
Not prescribed	517 (90,2 %)	107 (89,2 %)	0,724		0,013
Prescribed	56 (9,8 %)	13 (10,8)			
		Interferons (SC)			
Not prescribed	355 (97,8 %)	84 (91,3 %)	0,007*	4,2 (1,5–11,6)	0,142
Prescribed	8 (2,2 %)	8 (8,7 %)			
		Hydroxychloroquine			
Not prescribed	428 (74,7 %)	100 (83,3 %)	0,043*	0,6 (0,4–0,99)	0,077
Prescribed	145 (25,3 %)	20 (16,7 %)			
		IV CS			
Not prescribed	333 (63,5 %)	81 (68,6 %)	0,296		0,041
Prescribed	191 (36,5 %)	37 (31,4 %)			
		Short-acting insulins			
Not prescribed	460 (81,1 %)	91 (76,5 %)	0,245		0,044
Prescribed	107 (18,9 %)	28 (23,5 %)			
		Long-acting insulin			
Not prescribed	482 (85,0 %)	108 (90,8 %)	0,1		0,063
Prescribed	85 (15,0 %)	11 (9,2 %)			
		Oral hypoglycemic medications			
Not prescribed	505 (89,1 %)	115 (96,6 %)	0,011*	0,3 (0,1–0,8)	0,097
Prescribed	62 (10,9 %)	4 (3,4 %)			
		Diuretics			
Not prescribed	324 (57,1 %)	52 (43,7 %)	0,007*	1,7 (1,2–2,6)	0,102
Prescribed	243 (42,9 %)	67 (56,3 %)			
		Expectorants			
Not prescribed	259 (45,7 %)	70 (58,8 %)	0,009*	0,6 (0,4–0,9)	0,1
Prescribed	308 (54,3 %)	49 (41,2 %)			
Antiplatelets					
Not prescribed	439 (76,6 %)	94 (78,3 %)	0,684		0,015
Prescribed	134 (23,4 %)	26 (21,7 %)			
		Targeted therapy			
Not prescribed	265 (76,6 %)	70 (75,3 %)	0,790		0,013
Prescribed	81 (23,4 %)	23 (24,7 %)			

Note: The differences were considered statistically significant at p<0.05. ACE — angiotensin-converting enzyme; ARA — angiotensin II receptor antagonists; BB — beta-blockers; CCB — slow calcium channels blockers; CS — corticosteroids; ICS — inhaled corticosteroids; NSAIDs — non-steroidal anti-inflammatory drugs.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Conclusion

Thus, the analysis of the AKTIV and AKTIV 2 databases demonstrated that the incidence of CKD in COVID-19 patients is not higher than in the general population. AKI developed in 11.6 % of COVID-19 cases and was more common in patients with overweight and hyperglycemia. CKD and AKI increased the risk of hospital mortality in COVID-19 patients. It was also noted that, during 3 and 12 months of follow-up during the post-COVID period, mortality in CKD patients increased, and the highest difference in mortality rates was observed in 12 months. Patients who had AKI during coronavirus infection had high mortality rates in post-COVID period during first three months of follow-up. Certain drugs were efficient in reducing mortality rates in COVID-19 patients with CKD; therefore, existing drug regimens can be adjusted for this patient group. Specifically, ARB, NSAIDs, hydroxychloroquine, antihyperglycemic tablets, and mucolytics can be useful. Data analysis was retrospective, and analysis results can be used as a basis for randomised clinical trials in COVID-19 patients with CKD.

According to the authors, the limitations of this study are incorrect CRF filling-out (omissions, lack of information in primary medical records), which affects the data quality. Also, no multi-factor analysis was conducted in this study and it can be conducted at later stages. The study design did not provide for collection of pre-hospital medical information, that is why "CKD" refers to patients with an isolated GFR reduction of less than 60 mL/min/1.73 m^2.

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САХАРОСНИЖАЮЩАЯ ТЕРАПИЯ И ТЕЧЕНИЕ ПОСТКОВИДНОГО СИНДРОМА, ЕСТЬ ЛИ СВЯЗЬ?

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Hypoglycemic Therapy and the Course of Post-Covid Syndrome, is There a Connection?

Резюме

Сахарный диабет (как 1, так и 2 типа) считается одним из факторов риска тяжелого течения COVID-19 и смерти от этой инфекции. Перенесенная инфекция COVID-19 приводит к ухудшению контроля уже имеющегося сахарного диабета, прогрессированию предиабета в диабет, увеличению числа новых случаев диабета и росту удельного веса глюкокортикоид-индуцированного диабета, что значительно усугубляет течение постковидного синдрома для данной категории пациентов. Сахароснижающие препараты могут влиять на патогенез COVID-19, что может иметь значение для лечения пациентов с сахарным диабетом 2 типа и постковидным синдромом. В обзоре также представлены собственные данные о влиянии на постковидный синдром различных режимов приема пероральных сахароснижающих средств у лиц с сахарным диабетом 2 типа. Наблюдение показало, что использование ингибиторов дипептидилпептидазы-4 в составе лечебной стратегии у пациентов с сахарным диабетом 2 типа с перенесенной инфекцией COVID-19 ассоциировалось с уменьшением продолжительности и выраженности проявлений постковидного синдрома.

Ключевые слова: *сахарный диабет, инфекция COVID-19, постковидный синдром, ингибиторы дипептидилпептидазы-4, метформин*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Diabetes mellitus (both type 1 and type 2) is considered one of the risk factors for severe COVID-19 and death from this infection. Past infection with COVID-19 leads to deterioration in the control of existing diabetes mellitus, progression of pre-diabetes to diabetes, an increase in the number of new cases of diabetes and an increase in the proportion of glucocorticoid-induced diabetes, which significantly aggravates the course of post-COVID syndrome for this category of patients. Antihyperglycemic drugs may influence the pathogenesis of COVID-19, which may be of relevance for the treatment of patients with type 2 diabetes mellitus and post-COVID syndrome. The review also presents our own data on the effect of

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various regimens of oral hypoglycemic agents on post-COVID syndrome in people with type 2 diabetes mellitus. The observation showed that the use of dipeptidyl peptidase-4 inhibitors as part of a treatment strategy in patients with type 2 diabetes mellitus with a past COVID-19 infection was associated with a decrease in the duration and severity of post-COVID symptoms.

Key words: *diabetes mellitus, COVID-19 infection, post-COVID syndrome, dipeptidyl peptidase-4 inhibitors, metformin*

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ACE2 — angiotensin converting enzyme 2, GLP-1ra — glucagon-like peptide-1 receptor agonist, VAS — visual analogue scale, DPP-4 — dipeptidyl peptidase-4, IHD — ischemic heart disease, DPP-4i — dipeptidyl peptidase-4 inhibitor, SGLT-2i — sodium-glucose linked transporter-2 inhibitor, RCS — randomised controlled study, DM — diabetes mellitus, HbA1C — glycated hemoglobin

The novel coronavirus infection (COVID-19) caused by SARS-CoV-2 was first observed in China in December 2019 and very rapidly spread over the globe.

SARS-CoV-2 which causes this infection is an RNA virus; its single-stranded RNA genome is covered with a two-layer protein lipidic cover. The main receptor for the virus to attach to and penetrate in human cells is angiotensin converting enzyme 2 (ACE2), which is abundant in alveolar, vascular endothelium, myocardiocyte and a number of other cells (including pancreatic β-cells, thyrocytes, etc.).

The main route in humans is respiratory. Usually, symptoms develop over 5–6 days after contamination (sometimes 10–14 days). Moderate respiratory and general infection symptoms (fever, fatigue, headache, myalgias, possible nausea and vomiting) last for approximately 2 weeks. However, at this stage a majority of patients will develop a significant lung damage (viral pneumonia), which is complicated with acute respiratory distress syndrome, systemic inflammation response syndrome, multi-organ involvement, shock, and leads to death. Cytokine storm (hyperimmune inflammation) and thrombosis with vasculitis have a vital role to play in these complications. Often COVID-19 infection causes destabilization and exacerbation of underlying chronic diseases [1, 2].

For COVID-19 patients, diabetes mellitus (DM) is one of the most common comorbidities which is observed approximately in 20 % of patients. DM2 is known to have a negative impact on clinical outcomes [3]. Possible unfavourable outcomes include moderate and severe COVID-19 cases, higher ICU hospitalisation rates, a higher need in anti–IL-6 receptor antibodies (tocilizumab), and high mortality rates. Also, there are reports that hyperglycemia during COVID-19 is associated with poor outcomes and can be a negative predictor in patients with or without DM2. In patients with hyperglycemia, some drugs can be less efficient, especially tocilizumab, which is administered in patients with moderate to severe COVID-19 pneumonia. Thus, not only DM2, but also hyperglycemia can have negative impact on hospitalisation, clinical outcome and drug therapy, leading to poorer prognosis for COVID-19 patients [3, 4].

Prior severe viral respiratory infections (severe acute respiratory syndrome (SARS), H1N1) demonstrated possible long-term persistence of disorders which developed during the disease, including metabolic disorders. Same features are observed in COVID-19 patients. It was noted that some patients can have long-lasting (up to 12 months and longer) dislipidemia, insulin resistance, dysglycemia. Chronic post-virus syndrome associated with chronic fatigue, variable and non-specific myalgias, depression, anxiety, irritability, hyperthermia (including subfebrile hyperthermia and some episodes of febrile hyperthermia), sleep disturbances, and other manifestations (Fig. 1) are also frequent [5].

In Russian scientific literature, this set of symptoms is commonly called “post-COVID syndrome” (“post-COVID”, “long COVID” are the terms used abroad). Some authors believe that a suitable term is “chronic COVID” (taking into account the information on possible long-lasting persistence of viral particles in various tissues of the human body). The syndrome is applicable to persons who had COVID-19 infection (usually those patients whose disease started more than 28–30 days ago) and are still experiencing impaired well-being. Such patients account for at least 30–50 % in the group of COVID-19 survivors. Long-lasting symptoms can be observed not only in patients who had severe infection, but also in patients with moderate disease. Clinical manifestations can vary, sometimes they can be severe and cause disability to work. Patients with a history of COVID-19 are at a high risk of thromboembolic complications (including pulmonary artery thromboembolia, myocardial infarction, ischemic stroke) and death.

Слабость (Weakness)	95%
Одышка (Dyspnea)	78%
Миалгии (Mialgia)	68%
Сердцебиения (Palpitations)	68%
Сухой кашель (Dry cough)	65%
Тахикардия (Tachycardia)	62%
Диарея (Diarrhea)	56%
Гипертермия (Hyperthermia)	56%
Потливость (Sweating)	55%
Снижение аппетита (Reduction of appetite)	55%
Боли в грудной клетке (Chest pain)	53%
Артралгии (Arthralgia)	52%
Тошнота (Nausea)	48%
Дисменорея (Dysmenorrhea)	35%
Зуд кожи (Itching of the skin)	33%
Светобоязнь (Photophobia)	30%
Сухость глаз (Dry eyes)	27%
Кашель с мокротой (Cough with phlegm)	26%
Запор (Constipation)	20%

«Туман в голове», снижение внимания, затруднение принятия решений, когнитивные нарушения ("Fog in the head", decreased attention, difficulty making decisions, cognitive impairment)	85%
Нарушения сна (Sleep disorders)	68%
Нарушения памяти (Memory disorders)	65%
Тревожность (Anxiety)	58%
Раздражительность (Irritability)	52%
Депрессия (Depression)	48%
Головные боли (Headache)	40%
Тремор (Tremor)	40%
Апатия (Apathy)	38%
Нарушения обоняния (Olfactory disorders)	35%
Нарушения вкуса (Taste disorders)	33%
Невралгии (Neuralgia)	32%

Figure 1. *The frequency of some general somatic (left) and neuropsychiatric (right) symptoms among 3762 patients who had health problems after suffering a COVID-19 infection (adapted from Davis H.E. et al., 2021)*

At least 1/3 of subjects discharged from inpatient clinics where they were treated for COVID-19 infection, need re-admission during the next 6 months for various reasons. After COVID-19, a majority of patients require thorough multidisciplinary follow-up (Fig. 2); in some cases, adequate rehabilitation programs are useful [6].

In terms of pathophysiology, post-COVID syndrome is not a single clinical unit, but a set of symptoms and syndromes depending on a number of biological factors that require additional examinations.

Generally accepted factors include organ damage, persistent impairment in the regulation of inflammatory and immune response, as well as undiagnosed microvascular thrombosis and endothelitis. An assumption was made on the impact from some other causes: permanent tissue sources of SARS-CoV-2, reactivation of other viruses, dysfunction of the brain stem and/or nervus vagus, as well as autoimmunity activation due to molecular mimicry between pathogen and host proteins. Also, development of this condition can be facilitated by secondary infections (both bacterial or mycotic infections), sequelae of long-lasting hospitalisation, critical condition and intensive care, drug side effects (e. g., side effects of corticosteroids), social, economic, and psychological aspects. Besides, protein and micronutrient deficiency resulting from long-lasting hospitalisation and poor oral alimentation lead to nutritional deficiency in patients with severe COVID-19 [4, 6, 7].

A history of COVID-19 infection causes aggravation of pre-existing DM, pre-diabetes progression to diabetes, rise in the number of newly diagnosed DM cases and increase in the relative weight of glucocorticoid-induced diabetes, thus significantly worsening post-COVID syndrome in this patient group. Therefore, it is essential to use various hypoglycemic medications not only during COVID-19, but also during the post-infection period [3].

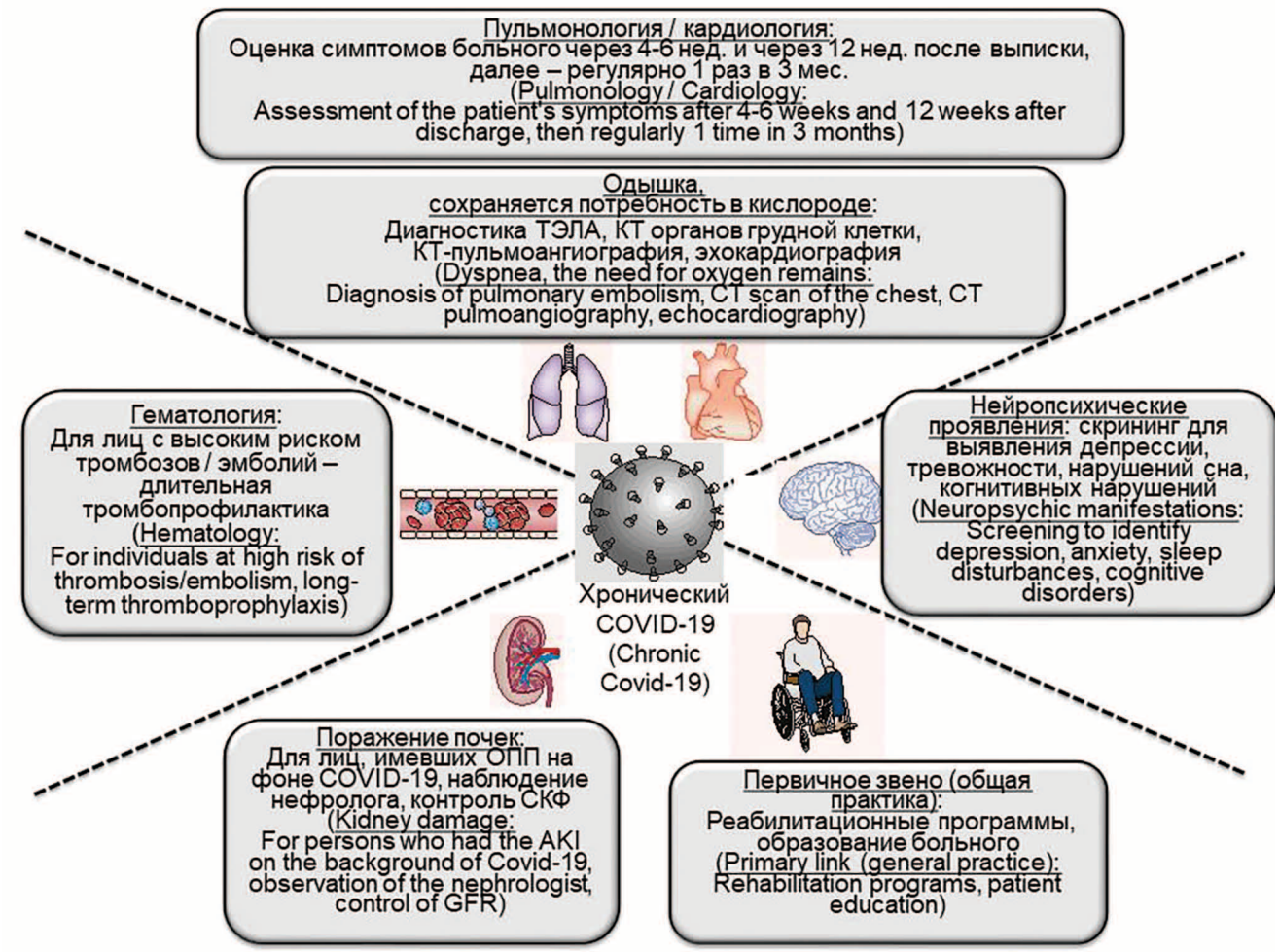

Figure 2. *Multidisciplinary approach to the COVID-19 survivor (adapted from Nalbandian A. et al., 2021)*
Note: PE — pulmonary embolism; CT — computed tomography; AKI — acute kidney injury; GFR — glomerular filtration rate

Antihyperglycemic drugs can affect COVID-19 pathogenesis, and these effects can be essential for the treatment of DM2 patients with the post-COVID syndrome. Currently, there are no results of large randomized controlled studies (RCS) evaluating the role of various classes of hypoglycemic agents in this patient group.

Available data on the use of hypoglycemic drugs relate to the COVID-19 period itself and not to the post-COVID syndrome. However, the data on the use of hypoglycemic agents during the acute period allow assuming that their effect in subjects with "chronic COVID" is similar; and further studies are needed.

At the moment, RCS DARE-19 is a topic that has been debated a lot; the study evaluates the effect of dapagliflozin, a sodium-glucose linked transporter-2 inhibitor (SGLT-2i), on the progress of COVID-19, but not post-COVID syndrome [8]. The study enrolled 1250 patients (mean age: 61 years) hospitalised with this infection (subjects in critical condition and those with marked respiratory distress were excluded). All subjects had at least 1 cardiac and metabolic risk factor (DM was observed in 51 % of patients, arterial hypertension — in 85 %). Subjects were randomized to take either dapagliflozin 10 mg/day or placebo. The study results did not demonstrate any reduction in the risk of respiratory, cardiovascular or renal dysfunction and mortality with dapagliflozin therapy; however, its satisfactory tolerability was verified. The DARE-19 data allow for reliable administration of SGLT-2i in mild to moderate COVID-19, while patients with severe disease should take these drugs with caution. Due to the risk of dehydration, diabetic ketoacidosis and acute kidney injury, SGLT-2i drugs are not indicated for severe coronavirus infection [8].

Available new data indicate that SGLT-2i have the same anti-inflammatory effect, including macrophage polarisation and reduction in proinflammatory cytokines levels [9-11]. A study of empagliflozin demonstrated that this drug inhibits acetylcholinesterase, reduces oxidative stress and positively modulates neurotransmission

and neuronal plasticity with a marked neuroprotective effect, which is an important factor in the management of patients with post-COVID syndrome [9, 11, 12].

Currently, there are reliable data on the adequate safety and satisfactory tolerability of dipeptidyl peptidase-4 inhibitors (DPP-4i) and insulin [13].

A number of experimental and epidemiological studies demonstrated positive potential biological effects of DPP-4i in COVID-19 infection; however, a favourable impact on disease prognosis was not proven. This class of drugs is well-tolerated even in severe infection cases. Therefore, DPP-4i can be continuously used in COVID-19 of various severity [13].

Dipeptidyl peptidase-4 (DPP-4), a membrane enzyme, plays an essential role in the immune system as an activated T lymphocyte marker and an expression regulator for numerous chemokines, including chemokine ligand 5 (motif C–C, CCL5), stromal cell factor 1 (also known as chemokine 12 of motif C-X-C — CXCL12), ligand 2 chemokine (CXCL2, also known as beta-regulated growth protein —GRO-b), and motif C-X-C of chemokine 11 (CXCL11). Earlier on some concerns were voiced as to an increased risk of viral infections when DPP-4 is inhibited; however, the data from clinical trials investigating the relations between DPP-4i and the risk of community-acquired pneumonia in DM2 patients do not support this assumption. Despite the fact that ACE-2 is the main SARS-CoV-2 receptor, DPP-4 can also bind to the virus (since DPP-4 molecule was previously identified as a receptor for Middle East respiratory syndrome (MERS) virus, taking into account the similarity of the causative agent, SARS-CoV-2 can also interact with this molecule). Theoretically, DPP-4 modulation can help in compensating cytokine-mediated COVID-19 complications [14]. Whether DPP-4i can affect the function of DPP-4 as a virus receptor is a matter of debate. In an in vitro study, the use of DPP-4i sitagliptin, vildagliptin or saxagliptin did not block coronavirus penetration into the cells; in an experiment with peripheral human blood the use of these drugs inhibited immute T killer response to the virus [15].

The studies of the use of DPP-4i in DM2 patients and COVID-19 are currently limited. In a retrospective case control study in Northern Italy, the use of sitagliptin during hospitalisation was associated with reduced mortality and improved clinical outcomes [16]. Another case series in Italy described the relations between DPP-4i therapy and statistically significant reduction in mortality rates; however, this result was obtained from 11 patients only (including one patient who died) [17]. In another study, DPP-4i therapy was associated with poorer results (mortality rates are not shown) in 27 DM2 patients who were treated with these drugs vs. 49 patients who were taking other antihyperglycemic agents [18].

The impact of DPP-4 inhibition on the T-cell function and T-cell-mediated inflammatory and immune reactions in COVID-19 patients require further investigation. More detailed studies are essential for characterisation of the role of DPP-4 inhibitors in patients with COVID-19 / post-COVID syndrome and DM2.

Insulin drugs are a main antihyperglycemic drug class to be used in severe COVID-19 (specifically for IV administration) for adequate glycemia control and reduction of the risk of acidosis. In a majority of cases, the need in insulin can be extremely high due to a negative impact from hyperinflammation on insulin resistance. Besides, insulin drugs have anti-inflammatory effect and reduce oxidative and inflammatory stress. During the acute phase of COVID-19 a lot of patients who took oral antihyperglycemic drugs need to transition to insulin, which should be administered subcutaneously also in outpatient settings. It will then be important to choose an adequate dose of insulin, to reduce the risk of hypoglycaemia, and possibly to retreat to oral antihyperglycemic drugs [2, 13].

In epidemiological studies of glucagon-like peptide-1 receptor agonists (GLP-1ra), drugs from this class demonstrated just neutral mortality effects in patients with DM and COVID-19. In severe COVID-19, reduced uptake of these drugs can be a result of loss of appetite and GIT side effects. At the same time, their possible anti-inflammatory effects are discussed [2, 3].

Metformin demonstrated a number of possible favourable effects in COVID-19 in epidemiological studies. This drug is considered relatively safe for outpatient patients with mild infection. Due to the risk of dehydration and lactic acidosis in hospitalised COVID-19 patients, it should be administered with caution; administration to ICU patients is not acceptable (this drug needs to be replaced with insulin). Continuous blood creatinine monitoring is required if this drug is prescribed.

Sulfonylurea medications for the use in DM patients with COVID-19 are the least studied drugs. Due to the risk of hypoglycaemia, special care should be taken even in mild COVID-19 cases. In moderate and severe infection, sulfonylurea medications should be avoided [2, 19].

The information on the use of thiazolidinediones in COVID-19 is very limited. Despite their possible organ protective effects, they are prescribed with care in patients with mild COVID-19 and are not used in moderate and severe infection [2, 19].

We would like to present our own case study of a DM2 patient with post-COVID syndrome. 53 DM2 patients (29 men and 24 women aged 64.6 ± 9.4 years) were followd up in Central City Clinical Hospital No.1 of Donetsk and the Railway Clinical Hospital of Donetsk (disease duration: 7.6 ± 1.8 years

with concomitant ischemic heart disease (IHD) in 58.6 % of cases). All patients had a history of COVID-19; 31 (58.5 %) patients had multisegmental pneumonia and were hospitalised (including 22 patients who were admitted to ICU); the mean duration of hospitalisation was 32 days. 20 (37.7 %) COVID-19 cases did not require hospitalisation. Prior to the infection, all patients were taking oral antihyperglycemic drugs. During hospitalisation, 29 (54.7 %) patients were transferred to insulin therapy, and their usual oral therapy was resumed later on. At the same time, patients were recommended to correct their lifestyle, to take appropriate organ protective and antithrombotic medications. 1 month after discharge from the clinic or inpatient therapy completion, all patients still had clinical manifestations of post-COVID syndrome, including lack of energy (91.8 %), shortness of breath (79.4 %), myalgias (72.8 %), dry cough (65.7 %), productive cough (27.3 %), hyperthermia (56.1 %), arthralgia (54.3 %), sleep/ memory/ attention disorders (70.9 %), irritability (52.2 %), depression (47.8 %), smell disorders (35.6 %). The intensity of clinical manifestations of post-COVID syndrome was assessed using a visual analogue scale (VAS).

There were 2 groups of patients depending on the antihyperglycemic drug regimen: group A (28 patients, metformin 1000–2000 mg daily + DPP-4i saxagliptin 5 mg daily, or sitagliptin 50–100 mg daily, or vildagliptin 50–100 mg daily) and group B (25 patients, same dose of metformin + sulfonylurea medications gliclazide 60–120 mg daily, or glimepiride 2–4 mg daily, or glibenclamide 5-–10 mg daily). There were no contraindications for these drugs. The groups were similar in demographics, baseline fasting glycemia, glycated hemoglobin (HbA_{1C}), COVID-19 severity, and post-COVID syndrome characteristics. The target HbA_{1C} was 6.5–7.0 %. Patients were followed up at least once every 1–2 months, with the average follow-up duration of 8 months.

Both groups tolerated the therapy well; there were no cases of therapy discontinuation due to side effects. The target HbA_{1C} was achieved in 21 patients (84 % of cases) in group A and 20 patients (80 % of cases) in group B, p = 0.7. During the follow-up period, post-COVID syndrome manifestations resolved or significantly improved (by 40.1 ± 1.5 % according to the VAS) was observed in 75 % (21 patients) in group A and 48 % (12 patients) in group B, p = 0.05. Hospitalisations due to any reason in group A were significantly less frequent than in group B (21.4 % vs. 48 %, 6 patients and 12 patients, respectfully); there were fewer tromboembolic episodes (3.6 % vs. 24 %, 1 patient vs. 6 patients, respectively), p = 0.05. The overall post-COVID syndrome duration in group A was 5.6 ± 0.9 months vs. 6.2 ± 1.2 months in group B, p = 0.04. The positive effect from DPP-4i on the progress of post-COVID syndrome did not depend on COVID-19 severity or presence/absence of IHD.

Therefore, in our observation the use of DPP-4i in the management of DM2 patients with prior COVID-19 infection was associated with reduced duration and lower severity of post-COVID syndrome.

Conclusion. For DM2 patients who suffer from post-COVID syndrome, it is essential to select adequate antihyperglycemic drugs. One of the promising antihyperglycemic class is DPP-4i, that can improve long-term prognosis in this patient category. Prospective RCSs in various populations of DM2 patients with post-COVID syndrome are required in order to assess potential improvement in the survival rates due to DPP-4 inhibition in subjects with COVID-19, which can apply to patients without DM as well.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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СЛОЖНОСТИ ВЕРИФИКАЦИИ ДИАГНОЗА ЛИХОРАДКИ КУ ПРИ ОТРИЦАТЕЛЬНЫХ РЕЗУЛЬТАТАХ ПЦР-ТЕСТИРОВАНИЯ

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Difficulties of Q Fever Diagnostic Verification at Negative PCR Testing Results

Резюме

Цель работы: продемонстрировать сложность верификации диагноза лихорадки Ку при отрицательных результатах ПЦР-тестирования на наличие в крови ДНК *Coxiella burnetii* и оценить встречаемость серологических маркеров среди пациентов, отобранных для настоящего исследования по совокупности клинико-эпидемиологических данных. **Материалы и методы:** у 111 пациентов методами иммуноферментного анализа и полимеразно-цепной реакции изучены образцы плазмы/сыворотки крови на наличие специфических антител и ДНК возбудителя. При выявлении антител к *C. burnetii* II фазы дополнительно проводились исследования на наличие IgG/IgA к коксиеллам I фазы, а также была изучена авидность специфических иммуноглобулинов класса G. **Результаты:** у 10 пациентов с отрицательными результатами полимеразно-цепной реакции были выявлены антитела к *C. burnetii*. В статье приведено подробное описание трех клинических случаев с лабораторным подтверждением инфицирования C. Burnetii на основании анализа полученных серологических профилей, титров специфических антител и оценки их авидности. **Заключение:** результаты исследования свидетельствуют о том, что отрицательные результаты ПЦР-тестирования не исключают у пациентов инфицирования *C. Burnetii*. В связи с этим, пациентам, у которых по клинико-эпидемиологическим данным не исключается лихорадка Ку, целесообразно назначение комплекса лабораторных исследований для верификации диагноза, предусматривающего не только исследования ДНК возбудителя, но и специфических антител. Для уточнения стадии заболевания и снижения риска развития осложнений коксиеллеза необходим мониторинг динамики титров антител к *C. burnetii* в I и II фазовых состояниях дифференциально. Оценка авидности антител будет полезна для понимания срока давности инфицирования *C. burnetii*.

Ключевые слова: *лихорадка Ку, коксиеллез, антитела к Coxiella burnetiid*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Aim of the work: to demonstrate the difficulty of verifying the diagnosis of Q fever with negative results of PCR (DNA of *Coxiella burnetii*) in the blood and to assess the occurrence of serological markers among patients selected for this study based on a combination of clinical and epidemiological data. **Materials and methods:** plasma/serum samples of 111 patients according to clinical and epidemiological data studied due ELISA and PCR for specific antibodies to *Coxiella burnetii* and DNA of pathogen. Additionally, in the presence IgG to *C. burnetii* phase II, IgG / IgA to phase I and the avidity of specific IgG were studied. **Results:** the specific antibodies to *C. burnetii* antigens at negative results of PCR detected in 10 cases. The article provides the description of three clinical cases for demonstration of difficulties of coxiellosis diagnosis with analysis of serological profiles, titers and avidity of antibodies. **Conclusion:** the results of the study indicate that negative results of PCR testing do not exclude *C. burnetii* infection. For patients who, according to clinical and epidemiological data, Q fever is not excluded, it is advisable to prescribe a complex of laboratory tests to verify the diagnosis, which includes not only studies of the pathogen's DNA, but also specific antibodies. To clarify the stage of the disease and reduce the risk of developing complications of coxiellosis, it is necessary to monitor the dynamics of antibody titers to *C. burnetii* in phase I and II phase states differentially.

Key words: *Q fever, coxiellosis, antibodies to Coxiella burnetii*

Conflict of interests

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PCR — polymerase chain reaction

Introduction

Q fever is a zoonosis, caused by the obligate intracellular bacterium *Coxiella burnetii*. It is widespread worldwide [1]. The disease was first described by Edward Holbrook Derrick in abattoir workers in Brisbane, Queensland (Australia) in 1933. He suggested calling this zoonosis "Q fever" ("Q" stands for "query") [2]. Specific features of Q fever include a variety of portals of entry, clinical polymorphism, subclinical course in a majority (up to 60 %) of patients and serious complications at the chronic stage [3]. The diversity of clinical manifestations in acute Q fever is associated with its mechanism of infection, infective dose and condition of the individual immune system [4].

The most common sources of infection are ruminant farm animals such as cattle, goats, and sheep. The mammals excrete Coxiella into the environment with feces, milk, and urine. The maximum amount of the causative pathogen is accumulated in the reproductive organs, resulting in premature births, abortions, and stillbirths in female animals [5]. Wild and domestic fowl can also be the source of infection, excreting the pathogen in feces. Ticks of different genera are reservoirs and carriers of the infectious agent in both natural and anthropogenic foci of Q fever [6–8]. High stability in the environment and resistance to various external factors allow for long-term persistence of the pathogen in the environment and spread of dusty aerosol with air currents over long distances. Humans can get infected with Q fever via fecal-oral, direct contact, and vector-borne routes of transmission [9, 10].

In Q fever, the incubation period varies 10 to 40 days, being 12 to 20 days on average. The disease onset is acute in 75 % of patients and is characterized by flu-like symptom complex. A polymorphic rash is observed in approx. 25 % of patients. Meningism events may occur at the height of fever. In acute Q fever, cardio-vascular involvement can be manifested as myocarditis, pericarditis, endocarditis, as well as heart rhythm disorders. Other possible signs of acute condition can be atypical pneumonia, hepatitis, pancreatitis, lymphadenopathy, extrapyramidal disorders, etc. Q fever progression to chronic form generally occurs in 3–6 months after acute infection and is reported in 5 % of patients on average. The chronic course is often complicated by Q fever endocarditis with heart valve involvement, aneurysms, vascular graft infection, vertebral osteomyelitis, hepatitis, etc. [11–16].

Based on molecular genetic, serological testing and the presence of clinical symptoms, some expert groups have attempted to describe diagnostic criteria for identification of acute and chronic stages of infection, assuming such terms as "proven," "probable," and "possible" in the latter case. A positive polymerase chain reaction (PCR) for pathogenic DNA in blood nearly always correlates with acute Q fever, however, the reaction quickly

becomes negative after initiation of antibiotics and build-up of specific antibodies. Therefore, PCR should be conducted within the first two weeks after clinical symptoms occur and until treatment with antibiotics is started. Nevertheless, this condition is rarely observed in practice [17, 18].

Serological testing is considered as the first-line diagnostic method. The immune response induces the production of antibodies to phase I and phase II *C. burnetii,* since the pathogen has antigenic variations associated with mutational change in lipopolysaccharide composition. The diagnosis of primary (acute) infection can be confirmed by a detected pronounced change over time in the levels of IgG and IgM phase II antibodies in paired sera taken at an optimal time interval. Antibodies to phase II *C. burnetii* are usually the first to be detected in the patient's blood and are most often detected 7–15 days after infection followed by a gradual decrease in levels, although remaining detectable for a long time [18]. The differential detection of immunoglobulins of different classes to *C. burnetii* antigens in phases I and II is of special importance. In some cases, the assessment of change in the levels of antibodies to phase I and II*C. burnetii* antigens in paired sera over time allows suggesting the stage of infection in a patient [19]. Titers of IgG to phase II antigens is generally greater than titers of IgG to phase I in current (acute) infection. In Q fever endocarditis and often in other manifestations of chronic condition, the titers (levels) of phase I *C. burnetii* IgG are almost always greater than the titers (levels) of phase II *C. burnetii* IgG [20]. Since there are still no clear diagnostic criteria for acute or chronic stages of the disease, some studies evaluating IgG avidity to *C. burnetii* in clinical practice have been recently published, suggesting that low-avid phase II *C. burnetiid* IgGs are in favor of recent infection. Higher levels of IgG avidity to phase I *C. burnetii* compared to IgG avidity to phase II *C. burnetii* are in favor of chronic Q fever [21, 22].

The study was aimed at demonstrating the difficulty of Q fever diagnosis verification in patients with negative PCR for *C. burnetii* DNA and assessing occurrence of serological markers in patients selected for the study by the aggregate of clinical and epidemiological data. The authors considered it necessary to provide a detailed description of three clinical cases of Q fever confirmed by serological methods, assessing profiles of antibodies to *C. burnetii.*

Materials and Methods

Blood plasma/serum samples were collected from 111 patients, being examined and treated in the Infectious Diseases Hospitals in Moscow from April till October 2021, and studied for clinical and epidemiological data (presence of fever, fact of tick biting/crawling, etc.).

If a patient had fever, rash, and the tick removed from the patient showed markers of transmissible pathogens, the blood plasma was tested by real-time PCR to detect pathogens of borreliosis, tick-borne encephalitis, tick-borne rickettsiosis, human granulocytic anaplasmosis and monocytic ehrlichiosis using the kits produced by Central Research Institute for Epidemiology of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing: AmpliSens® TBEV, *B. burgdorferi sl, A. phagocytophilum, E. chaffeensis/E.muris*-FL, AmpliSens® *Coxiella burnetii*-FL, AmpliSens® *Rickettsia* spp. SFG-FL.

The patients' blood serum samples were also tested using reagent kits authorized in the Russian Federation for the following purposes:

- for screening of IgG/IgM to Q fever pathogen (kits: *Coxiella burnetii* ELISA IgG, *Coxiella burnetii* ELISA IgM, manufactured by Vircell S.L, Spain);
- for confirmation and differential identification of different classes of antibodies to phase I and II *Coxiella burnetii* using reagent kits, manufactured by Virion/Serion Institute, Germany: Virion/Serion *Coxiella burnetii* Phase I IgG, Virion/Serion *Coxiella burnetii* Phase I IgA, Virion/Serion *Coxiella burnetii* Phase II IgG, Virion/Serion *Coxiella burnetii* Phase II IgM;
- for determination of Borrelia IgM/IgG, using kits: Anti-*Borrelia* ELISA (IgM) and Anti-*Borrelia* ELISA (IgG), manufactured by EUROIMMUN AG, Germany;
- for determination of *Rickettsia conorii* IgG/IgM using kits: *Rickettsia conorii* ELISA IgG/IgM (Vircell S.L, Spain).

The parameters of IgG avidity to phase I and II *C. burnetii* antigens (if any) were additionally studied according to the earlier described procedure [22].

The patients' blood serum samples were studied on days 1–2 of presentation, and five patients underwent serological testing in paired sera 14 to 30 days afterward.

All patients were prescribed complete blood count and blood chemistry test, urinalysis, as well as other necessary additional investigations to clarify their condition.

Results

The screening study revealed the presence of specific antibodies to *C. burnetii* in the serum of 10 patients out of 111 patients screened, with negative PCR results (*C. burnetii* DNA in blood plasma). Seropositive patients included 5 men and 5 women older than 54 years. All patients sought medical advice in May–June 2021 and

reported a history of contact with ticks (one patient removed ticks from a domestic animal). While taking epidemiological anamnesis, it was found that prior to presentation, the patients were in one of the regions close to the Moscow Region (Tula, Yaroslavl, Vladimir, Ryazan regions), and four patients were in the Moscow Region. One patient reported multiple cases of tick sucking prior to 2020.

Five of ten seropositive patients received inpatient treatment. They were admitted to hospital on day 5–30 of the disease with the following referral diagnosis: community-acquired pneumonia (two cases), tick-borne borreliosis (one case), tracheobronchitis (one case), and tick-borne encephalitis (one patient). The main complaints were increased body temperature 37.8 °C to 39 °C and weakness. Three patients had history of arthralgia, and two patients had history of erythema migrans. In two patients, the complete blood count demonstrated moderate thrombocytopenia (up to 130×10^9/L) and decreased hemoglobin (up to 105 g/L).

The patients sought outpatient consultation after tick sucking without any active complaints, and only one of them had erythema migrans.

In 6/10 examined patients, blood serum testing revealed both antibodies to Q fever pathogen and arthropod-borne infection antigens: to Rickettsia conorii (one patient), to tick-borne encephalitis virus antigens (two patients), and to Borrelia antigens (three patients). Antibodies to *C. burnetii* alone were found in four patients.

Below are presented clinical cases from our clinical practice that demonstrate the complexity of Q fever verification.

Clinical case No. 1

Patient M., female, 62 years of age, was admitted to the Infectious Diseases Hospital on day 12 of disease. The patient had complaints of fever up to 39 °C, marked weakness, non-productive cough, periodic dizziness, sensation of heaviness in the chest, and shortness of breath on exertion. The patient found a sucking tick in the popliteal space on May 2, 2021, while staying at her summer cottage in the Yaroslavl Region. No testing of the tick for the markers of arthropod-borne infections was conducted; the patient had no erythema. On day 3 after tick sucking, the patient noted fever up to 39 °C. One week before hospitalization, after professional medical advice, the patient received amoxicillin 500 mg, twice daily, with no perceptible effect. Due to persisting high fever, patient M. was admitted to hospital by the ambulance crew with diagnosis: Community-acquired pneumonia, condition post tick sucking.

At admission, the patient's condition at admission was considered to be of moderate severity. No swelling, hemorrhages, or exanthems. On examination, there was a crusty ulcer of 3 mm in diameter, no itching or erythema on the skin in the popliteal space. Peripheral lymph nodes were not palpable. On auscultation, there were no rales in the lungs; vesicular breathing; decreased breath sounds on the left; respiratory rate: 23 per minutes. Arterial blood pressure: 125/85 mm Hg; pulse rate: 80 bpm. The liver and spleen were not palpable. Bowel and bladder functions were within normal.

Complete blood count: WBCs 5.5×10^9/L; platelets 344×10^9/L; lymphocytes 1.73×10^9/L; hemoglobin 113 g/L; RBCs 3.42×10^{12}/L. The blood chemistry test found no abnormalities: C-reactive protein 45 mg/L (normal limit: up to 5 mg/L); fibrinogen 6.9 g/L (normal limit: up to 4 g/L). PCR test for pathogens of tick-borne encephalitis, anaplasmosis, coronavirus infection, type A and B influenza: negative. No IgG and IgM to *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were detected. IgG avidity to cytomegalovirus: 84 % (highly avid, postinfectious).

Chest computed tomography (CT) as of May 16, 2021, showed a pattern of bilateral interstitial pneumonia with primary involvement of the left lung. At hospital, the patient was prescribed background intravenous detoxification and antibiotic therapy with ceftriaxone 1 g twice daily, parenterally.

Tests for markers of tick-borne infections, including Q fever, were conducted for epidemiological indications (tick sucking). Molecular genetic markers of pathogens of borreliosis, tick-borne encephalitis, tick-borne rickettsiosis, human granulocytic anaplasmosis, human monocytic ehrlichiosis, Q fever were not detected.

The blood serum test as of May 18, 2021, found anti-Borrelia IgM, cut-off index (COI) = 2.5 (positive ELISA at COI > 1.1), Borrelia IgG: negative. ELISA using test kits manufactured by Vircell S.L found phase II *C. burnetii* IgM in the titer of 1 : 100, in the absence of specific IgG. The second sample tested two weeks after the first sampling revealed the following: Borrelia IgM, COI = 2.9: positive; Borrelia IgG: negative; phase II *C. burnetii* IgM: not detected; phase II *C. burnetii* IgG: positive; final positive titer: 1 : 200. IgG avidity index to phase II *C. burnetii* was 32.2 % (low-avid antibodies), indicative of recent infection.

Blood serum samples were additionally tested by ELISA using the test-systems, allowing for differential detection of antibodies of different classes to phase I and II *C. burnetii* antigens, manufactured by Virion/Serion Institute. Tests of the first and second samples of blood serum from patient M. did not find phase I *C. burnetii* IgG/IgA; however, the test of the first sample revealed phase II *C. burnetii* IgM with optical density (OD) = 0.897 AU (positive ELISA result at OD > 0.680 AU). After treatment initiation, the second blood serum

sample showed a decrease in OD to controversial (borderline) result for IgM. Moreover, the second sample demonstrated an increase in OD signals compared to the first sample while testing for phase II *C. burnetii* IgG to positive (titer 1 : 200). The obtained laboratory findings were in favor of recent co-infection (ixodic tick-borne borreliosis + Q fever).

After treatment, the patient was discharged in satisfactory condition under supervision of the infectious disease physician with recommendations to conduct dynamic testing for specific antibodies to *C. burnetii* for a long time, as well as other investigations.

This clinical case demonstrates the difficulty of Q fever (co-infection) diagnosis without specific laboratory tests.

Clinical case No. 2

On April 13, 2021, patient K., 71 years of age, was admitted to the Infectious Diseases Hospital by the ambulance crew with complaints of dry cough and pyretic fever for one-month, preliminary diagnosis: acute respiratory viral infection, tracheobronchitis, unspecified fever. The patient considered himself to have been ill since March 15, 2021, when the body temperature increased to 39 °C. Earlier, the patient received inpatient treatment for diagnosis: exacerbation of chronic prostatitis and was discharged with improvement; however, he had low-grade fever and complained of lower back pain irradiating to the right hip joint and thigh. On April 5, 2021, the patient consulted an outpatient physician with complaints of fever up to 39 °C, cough, weakness, and lower back pain. Outpatient treatment with levofloxacin, arbidol, and Lasolvan® provided no observable effect. During treatment, the patient underwent chest tomography and PCR for SARS-CoV-2 twice with negative results.

According to the patient's life history: chronic coronary heart disease, functional class 3 angina pectoris, grade 2 hypertension disease, atherosclerosis of aorta and cerebral vessels, chronic pyelonephritis, chronic bronchitis, duodenal ulcer, liver fibrosis. In 2013, the patient received inpatient treatment for spinal injury, and has had lower back pain since then. In 2014, the patient received inpatient treatment in the TB hospital with a diagnosis of nonspecific osteomyelitis; however, no data suggestive of tuberculosis infection were obtained. During several years prior to presentation to the Infectious Diseases Hospital, the patient removed ticks while staying at his summer cottage in the Vladimir Region.

At admission, the patient's condition was considered to be of moderate severity. Body temperature: 38.7 °C. Dry rales in the lungs; heart sounds were muffled and rhythmic; no peripheral edema or hemorrhages. Respiratory rate: 18 per minute; blood pressure: 130/80 mm Hg. Peripheral lymph nodes were not palpable. No signs of scratching or bites. The abdomen was soft on palpation and non-tender in all regions. On palpation, the enlarged dense liver protruded below the costal margin for 4 cm; the spleen was enlarged. Formed, regular stool.

Taking into account the presence of leukocyturia, erythrocyturia, bacteriuria in the urinalysis, urinary tract infection was suspected and antibiotic therapy with ceftriaxone 1 g twice daily intramuscularly and probiotics was prescribed. The body temperature returned to normal on day 2 of the patient's stay in hospital. The complete blood count showed moderate thrombocytopenia (121×10^9/L); the blood chemistry test demonstrated increased alkaline phosphatase activity (240 U/L) and C-reactive protein (15 mg/L). The electrocardiography examination found left bundle branch block.

Based on the combination of life history and investigation data, it was decided to perform additional blood serum testing for specific markers of arthropod-borne infections, including Q fever. The PCR test did not reveal genetic markers of pathogens of borreliosis, tick-borne encephalitis, tick-borne rickettsiosis, human granulocytic anaplasmosis, human monocytic ehrlichiosis, Q fever. However, the blood serum testing by the ELISA method detected phase II *C. burnetii* IgG (OD = 1.121 AU, positive result: >0.78 AU) in the absence of phase II *C. burnetii* IgM. Final positive titer: 1 : 500. IgG avidity to phase II *C. burnetii* was 76% (highly avid). To clarify the stage of Q fever, an additional test for phase I *C. burnetii* IgG/IgA was conducted. The blood serum test found phase I *C. burnetii* IgA with OD = 1.500 AU (positive result: >1.081 AU), titer 1 : 800. The obtained laboratory data were in favor of probable chronic Q fever. On April 19, 2021, the patient was discharged in satisfactory condition under supervision of the infectious disease physician with recommendations to conduct dynamic testing for specific antibodies for a long time, as well as other investigations.

This clinical case demonstrates the difficulty of recognizing Q fever in chronic stage without specific laboratory tests, and the lack of physician suspicion of Q Fever, as in the clinical case described above.

Clinical case No. 3

On June 2, 2021, patient E., 55 years of age, presented to the Consulting and Outpatient Department of the Infectious Diseases Hospital, Moscow due to Borrelia DNA detected in the tick, which the patient removed on May 6, 2021. No testing of the tick for *C. burnetii* and Rickettsia DNA was conducted. At presentation, the patient had no complaints. The tick sucking took place in the Vladimir Region. The patient did not receive medical

therapy. According to medical history, the patient was earlier treated for chronic HCV infection. When examining the tick sucking site in the right axillary space, no erythema was found. Due to detection of Borrelia DNA in the tick, patient E. was prescribed antibiotic therapy with amoxicillin/clavulonic acid at a dose of 875/125 mg twice daily for 10 days.

Taking into account the fact of tick sucking, patient E. underwent additional blood plasma/serum tests for the presence of markers of tick-borne infections, including Q fever. The blood test did not reveal genetic markers of pathogens of borreliosis, tick-borne encephalitis, tick-borne rickettsiosis, human granulocytic anaplasmosis, human monocytic ehrlichiosis, Q fever. At the same time, the blood serum test by the ELISA method using the test system, manufactured by Vircell, as of June 2, 2021, revealed phase II *C. burnetii* IgG, COI = 13.6; final positive titer: 1 : 500. The paired blood serum sample test, conducted two weeks after the first sample, showed a slight decrease in COI to 11.1; final positive serum titer: 1 : 500. Phase I *C. burnetii* IgG were determined in both samples: at blood serum dilution 1 : 500, signal OD (first sample) was 0.948 AU (cut off = 0.670); in the second sample, OD = 0.866. Phase I *C. burnetii* IgA and specific IgM to the pathogen were not detected.

In the first sample, IgG avidity to phase I *C. burnetii* was 87 %, phase II *C. burnetii* IgG was 74.5 %. Two weeks later, the avidity values were almost the same: 85.8 % and 77.2 %, respectively.

The high level of class G antibodies to the pathogen in phase I state and highly avid IgG (with an excess of phase I versus phase II IgG avidity) were in favor of long-term infection with *C. burnetii* in the patient, but this fact was established for the first time. According to the combination of laboratory data, the chronic stage of Q fever in patient E. cannot be ruled out.

The patient was recommended serological monitoring of antibodies to *C. burnetii* and other necessary investigations to prevent complications.

Discussion

The absence of pathognomonic clinical signs of Q fever and the frequent subclinical course of the disease leads to the fact that it remains undiagnosed in the majority of cases. At the same time, *C. burnetii* infection can lead to severe complications, sometimes fatal for the patient. The disease etiology cannot be proven without specific laboratory diagnostic methods. The laboratory examination is indicated to individuals based on the epidemiological anamnesis (work in animal breeding; husbandry and care of cattle and small ruminants, poultry; consumption of raw milk, dairy and meat products that have not been sufficiently processed); patients with fever, intoxication syndrome, respiratory involvement, hepatomegaly, jaundice syndrome, exanthems, hemostasis, gas exchange disorders, and complications [16]. This list of clinical signs can be supplemented by the observations of other leading researchers in the disease area, especially those who managed patients during and after the largest outbreak of Q fever in the Netherlands in 2007–2010, when the number of infected people exceeded 4,000 [23]. Due to the high cost of necessary diagnostic kits, in practice, they are often limited either to detection of antibodies (most often without differential assessment of immunoglobulins to Coxiellae in two phase states) or to detection of pathogen DNA.

The given study demonstrated that Q fever can be found in the Moscow and neighboring regions; however, its diagnosis is complicated. The PCR test did not reveal pathogen DNA in any of the tested blood plasma samples. In most cases, blood sampling from the patients who were seropositive to *C. burnetii* was performed after the start of antibiotic therapy or long after the disease onset. Therefore, when making a decision on the absence of infection, we did not consider a negative PCR to be definitive. The chronic phase is as important to be recognized as the acute phase, since the risk of life-threatening complications increases with disease progression. Therefore, a two-stage study was conducted: the first stage included serological screening for phase II *C. burnetii* IgG/IgM, and if a positive result was obtained, the study was supplemented by detection of phase I *C. burnetii* IgA/IgG, as well as assessment of antibody avidity. Q fever was serologically confirmed in 10 patients, since there was an opportunity to conduct thorough study of the clinical material in the presence of relevant diagnostic kits. The assessment of IgG avidity contributed to the disease stage clarification.

In the described clinical case No. 1, primary acute Q fever (concomitant infection of borreliosis) was confirmed in laboratory settings by seroconversion of antibodies to phase *II C. burnetii* antigens. Notably, there were specific IgM detected in the first sample, while a switch in the immunoglobulin synthesis from IgM to IgG was observed in the second sample. Low-avid IgG were indicative of a recent infection with Coxiellae, which was likely to have occurred via a vector-borne pathway. In this case, the main clinical symptoms included fever, weakness, and signs of pneumonia.

It is necessary to pay special attention to the elderly patients and those complaining of long-term fever in order to rule out *Coxiella burnetii* infection. Collection of complete medical history of the current condition, past medical history, and epidemiological data gains special importance In clinical case No. 2, one of the possible clinical manifestations of chronic Q fever was described, probably during exacerbation, taking into

account aggravation of the patient's condition and current fever. This has found laboratory confirmation in the form of increased levels of antibodies to the lipopolysaccharide complex of phase I *C. burnetii,* which quite often correlates to the development of Q fever complications, especially in the cardiovascular system [21]. Specific IgGs were considered to be highly avid, which further confirmed long-term infection that had not been previously recognized in time and probably caused a number of complications.

Clinical case No. 3 is a good example of obliterated and unpronounced signs of Q fever. The presence of phase I *C. burnetii* IgG and highly avid IgG were suggestive of long-term infection in the patient. This fact was established occasionally.

Conclusions

In some cases, the aggregate of clinical and epidemiological data did not allow suspecting Q fever in a patient. The disease etiology cannot be established without specific laboratory diagnostic methods. However, the laboratory diagnosis of Q fever is also accompanied by certain difficulties, since a negative PCR for *C. burnetii* DNA does not allow ruling out infection in a patient. Moreover, regardless of the disease stage, the leading expert working groups on Q fever recommend long-term serological monitoring for up to 5 years to prevent severe complications and relapses [11]. In this regard, the importance of additional serological studies is in no doubt: all patients with suspected Q fever and those previously diagnosed should be tested for the presence of specific antibodies to phase I and II *C. burnetii.*

The study of the serological profile with differential assessment of titers (levels) of antibodies of different classes to the pathogen and their avidity can give the treating physician a lot of valuable information about the infection course. In our opinion, expanded studies for markers of Q fever (pathogen DNA; titer of phase I and II *C. burnetii* IgA, IgM, IgG; avidity index) in the group of individuals affected by the tick bite, as well as among patients with fever and unknown disease etiology, are promising. The data from the study will allow improving the diagnostic algorithm of Q fever and patient management strategy in cases of suspected Q fever.

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ДРАМАТИЧЕСКИЙ ИСХОД ПОЗДНЕЙ ДИАГНОСТИКИ ХРОНИЧЕСКОГО АУТОИММУННОГО ТИРЕОИДИТА С ПЕРВИЧНЫМ ГИПОТИРЕОЗОМ ТЯЖЕЛОЙ СТЕПЕНИ

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The Dramatic Outcome of the Late Diagnosis of the Chronic Autoimmune Thyroiditis with the Severe Primary Hypothyroidism

Резюме

Статья посвящена разбору клинического случая поздней диагностики тяжелого гипотиреоза. Приведен обзор так называемых «клинических масок» гипотиреоза, затрудняющих диагностику. Акцентируется внимание на необходимости своевременного включения в план комплексного обследования коморбидных пациентов анализов уровня тиреотропного гормона гипофиза и гормонов щитовидной железы. Показано, что несвоевременное начало заместительной терапии гипотиреоза ассоциировано с плохим прогнозом.

Ключевые слова: *гипотиреоз, хронический аутоиммунный тиреоидит, тиреотропный гормон, полисерозит, кишечная непроходимость*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article is devoted to the analysis of a clinical case of the severe hypothyroidism. A review of the "clinical masks" of the hypothyroidism is presented. The examination of the polymorbid patients should include the level of thyroid-stimulating hormone and thyroid hormones. The untimely initiation of substitution therapy is associated with a poor prognosis, and the early start of the treatment is a guarantee of saving the life of a patient with severe hypothyroidism.

Key words: *hypothyroidism, chronic autoimmune thyroiditis, thyroid-stimulating hormone, polyserositis, intestinal obstruction*

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NYHA: New York Heart Association: SpO_2: blood oxygen; BP: blood pressure; HT: Hashimoto's thyroiditis; TPO-AB: thyroid peroxidase antibody; posterior LV wall: left ventricle posterior wall; IHD: ischemic heart disease; APV: artificial pulmonary ventilation; LV: left ventricle; MSCT: multispiral computed tomography; ACS: acute coronary syndrome; ACE: acute cerebrovascular event; GFR: glomerular filtration rate; T3: triiodothyronine; T4: thyroxine; TTH: thyrotropic hormone; TRH: thyrotropin-releasing hormone; US examination: ultrasound examination; EF: ejection fraction; CKD: chronic kidney disease; CHF: chronic heart failure; RR: respiratory rate; HR: heart rate; ECG: electrocardiogram; CEA: cardiac electrical axis

Hypothyroidism is a clinical syndrome caused by persistent thyroid hormone depression, resulting in various disorders in all body organs and systems [1].

A majority of scientific papers dedicated to this topic in the 20th century start with a historical perspective that the term was introduced by William Withey Gull, an English Surgeon in Ordinary to the King, who in 1873 described myxedema in thyroid gland atrophy; he proposed the term "myxedema" in 1878. William Miller Ord [2].

According to W. Gull, hypothyroidism was the lack of substance secretion from thyroid gland [3]. These substances were not yet called hormones. The chemical formula of thyroxine (T4) was discovered approximately 50 years later, and that of triiodothyronine (T3) — approximately 80 years later. Accurate determination of thyroid hormones in patients' blood was possible only 100 years later [2].

In 1882–1883, surgeons E.T. Kocher and J.L. Reverdin found the relationship between thyroidectomy and a set of symptoms of hypothyroidism. Later, attempts were made to treat post-surgery myxedema with thyroid tissue transplantation (M. Schiff, 1884) and ovine thyroid tissue extract (G.R. Murray, 1891). Thus, hypothyroidism can be seen as the first endocrine disorder, where replacement therapy was used.

Taking into account that hypothyroidism has been studied for over one and a half centuries, the publications and studies dedicated to this topic are abundant. Medicinal products to treat this condition have improved: starting from the use of bovine thyroid extract and up to available lactose-free and encapsulated synthetic levothyroxine gels. Thyroid associations publish recommendations on the management of various types of hypothyroidism almost annually [4].

Globally, over 665 million people have hypothyroidism and other thyroid gland disorders; 1.5 billion people are at risk of developing iodine deficiency. The annual increase in the number of thyroid disorders makes 5 % [1].

According to the World Health Organisation (WHO), hypothyroidism takes the second place in terms of the incidence among endocrine disorders (after diabetes mellitus). According to various data, in Russia, 58.8 % of patients with thyroid gland pathologies have hyperthyroidism and 35.3 % have hypothyroidism [5]. When comparing these data with foreign statistics, it becomes clear that the incidence of manifest hypothyroidism in the United States of America (USA) varies from 0–3 % to 3–7 %, in Europe — from 0–2 % to 3–5 %, depending on the method used [6].

According to metaanalyses conducted in ten European countries, the incidence of undiagnosed hypothyroidism, including both manifest and mild cases, is approximately 5 %. The differences in iodine status affect the incidence of hypothyroidism. Hypothyroidism is more frequent in women, patients of over 65 years old, in patients with autoimmune disorders (for instance, type 1 diabetes mellitus, autoimmune atrophic gastritis and gluten-sensitive enteropathy, and can be accompany numerous autoimmune diseases. People with Down's syndrome or Turner syndrome are at a higher risk of hypothyroidism.

In terms of pathogenesis, hypothyroidism can be primary, secondary, and tertiary. Secondary and tertiary hypothyroidism is often called "central (pituitary-hypothalamic) hypothyroidism"; they are a result of thyrotropic hormone (TTH) and thyrotropin-releasing hormone (TRH) deficiency. In a majority of cases, central hypothyroidism is associated with deficiency of other tropic hormones of the anterior pituitary gland; it develops in inflammatory, traumatic or destructive disorders affecting the pituitary-hypothalamic area (necrosis, tumour, cysts, hemorrhage, surgeries, radiation exposure) [1]. Central hypothyroidism is rare, accounting for no more than 1 % of all hypothyroidism cases. This condition equally affects men and women; the incidence in the population varies from 1:16,000 to 1:100,000 people depending on age and ethiology [7].

Primary hypothyroidism has high clinical significance and incidence; the most common causes are Hashimoto's thyroiditis, thyroid gland surgeries, treatment

with radioactive iodine (I-131) or radiation therapy of neck tumours [5]. Usually these conditions cause persistent irreversible deficit of thyroid hormones. For some decades now, wide use of some drugs, specifically of phenytoin, glucocorticosteroids, antibiotics, barbituates, diuretics, amiodarone, led to a significant increase in the incidence of drug hypothyroidism which sometimes requires therapy discontinuation [8].

Primary hypothyroidism is one of the most frequent endocrine disorders. According to a large population study, The Third National Health and Nutrition Examination Survey (NHANES-III), the incidence of primary hypothyroidism was 4.6 % of the population. The thyroid peroxidase antibody (TPO-AB) carrier status is observed in 10 % of women and depends on the ethnic composition of the population [7].

Usually hypothyroidism is permanent; however, in a number of thyroid gland diseases it can be transient [9]. In some disorders (subacute, postpartum, cytokine-induced thyroiditis) or in case of exposure to some drugs (excessive doses of iodine, thyrostatics), transient hypothyroidism can develop which resolves along with the natural course of the disease, or once the exposure from the trigger stops (e.g., after thyrostatic drug discontinuation) [10].

There is also peripheral hypothyroidism which is caused by tissue and organ resistance to thyroid hormones or thyroid hormone antibodies. In real life, this condition is extremely rare [1].

In terms of severity, hypothyroidism can be

- Asymptomatic (or latent) — clinical symptoms can be absent or can be very mild; blood TTH levels are high against the background of normal thyroid hormone levels. This conditions is diagnosed in 10–20 % of the population. Approximately 5 % of asymptomatic hypothyroidism cases are known to progress to manifest hypothyroidism annually, and within 4–8 years this conditions affects 20–50 % of patients.
- Manifest hypothyroidism — this condition is associated with clinical manifestations, high TTH levels and low blood thyroid hormone levels.
- Severe (long-lasting) hypothyroidism progressing to hypothyreoid (myxedema) coma [1].

Myxedema coma is caused by the absence of any hypothyroidism therapy or an inadequate replacement therapy doses. Hypothyreoid coma is characterised by progressing brachycardia and arterial hypotension, hypothermia, urinary retention, bowel obstruction. Cerebral blood flow slows down, and hypercapnia develops, resulting in impaired consciousness, catatonia, and coma. Even with timely treatment, hypothyreoid coma is associated with high mortality rates (50–80 %) [1].

In a prospective study conducted by Cesar Milstein Clinic (Buenos Aires, Argentina), it was demonstrated that manifest hypothyroidism during hospitalisation is reliable associated with high mortality rates [11].

Hormone tests (TTH and free T4 levels) are enough to diagnose hypothyroidism and identify an adequate replacement therapy. Other examination methods (thyroid gland ultrasound, elastography, isotopic scintigraphy, thyroid tissue antibodies, etc.) help in identifying the cause of hypothyroidism [1].

On the one hand, hypothyroidism diagnostics can seem very simple and readily available, but on the other hand, very often hypothyroidism is concealed by numerous somatic, gynaecologic and other endocrine disorders. This is why early diagnostics of this multifaced disease is difficult [5].

Clinical manifestations of hypothyroidism are individual for each and every patient. One patient may have no hypothyroidism manifestations at all, while another person with just a slight increase in TTH level will have numerous complaints [12]. It is also worth mentioning that there is no strict correlation between clinical manifestations of hypothyroidism and TTH and thyroxine levels; thus, diagnostic search becomes even longer.

The variety of signs and symptoms of manifest hypothyroidism is due to a wide spectrum of thyroid hormone impact on cell metabolism. In addition to energy metabolism, they regulate carbohydrate, fat and protein metabolism, thus affecting all organs and systems. Very often the lack of specific clinical manifestations of hypothyroidism delays diagnosis. For a long time patients may be followed up by various medical professionals for a syndrome that has manifestations and is diagnosed earlier than any other syndromes. As a rule, therapy of such cases is inefficient, since the management is aimed towards covering conditions and not hypothyroidism itself [1].

Early symptoms of thyroid insufficiency are nonspecific, in a number of cases the disease is asymptomatic (it is true specifically for subclinic hypothyroidism). Early signs of this condition include chills, fatigue, atony, clonus, constipations, excessive menstrual bleeding [1].

Currently, there are 11 known groups of covering conditions of hypothyroidism:

- Therapeutic: main symptoms are arterial hypertension or hypotension (less frequent); cardiac insufficiency events due to impaired miocardial contractility; dyslipidemia; arthropathy; polyserositis; myocarditis; pyelonephritis; hepatitis; biliary dyskinesia, and bowel hypomobility.
- Haematological: anemias (iron deficiency, normochromal and hypochromic anemia).
- Surgical: increased lithogenicity of bile with cholelithiasis; bowel obstruction.

- Gynaecologic: opsomenorrhea; excessive menstrual bleeding; metrorrhagia; amenorrhea.
- Endocrine: obesity; erectile dysfunction; decreased interest; delayed puberty.
- Neurological: myopathy; polyneuropathy; encephalopathy.
- Dermatological: alopecia; pilosis.
- Psychiatric: depression; myxoedema delirium; drowsiness; agrypnia.
- Otorhinolaryngologic: hardness of hearing; sinusitis; laryngitis.
- Gastroenterological: anorexia; kolitis; cholecystitis.
- Nephrological: pyelonephritis.

Diagnostics of hypothyroidism in patients of over 60 years old can be quite challenging, and the incidence of hypothyroidism in this group is 6–12 %. This is primarily due to a large number and severity of comorbidities in this group of patients, the need to adjust such conditions, and the overall psychosomatic status of patients [5].

The clinical features of hypothyroidism in elderly patients include:

- Slow and gradual development of symptoms unnoted by the patient and persons around him/her.
- Various manifestations of hypothyroidism involving almost any organ and system that prolong diagnostic search and delay drug management initiation play a role in development of complications.

Elderly people with gradual hypothyroidism progression are followed up by various medical professionals who have to deal with numerous symptoms: hoarseness, loss of hearing, stiff muscles, hand numbness and weakness, unsteady gait, dry skin, anemia, constipation. These common and non-specific symptoms are frequently seen as signs of ageing [5].

Let's discuss a case study of hypothyroidism that was diagnosed at a late stage and was associated with bowel obstruction, cardiac failure, pyelonephritis, anemia, hypothyreoid coma, and, eventually, death.

Case study

Patient Yu., 60 years old, was admitted to the therapeutics department of a multi-profile clinical hospital in September 2020 and was complaining of stabbing abdominal pain with unknown localisation, diarrhea for 4 days before hospitalisation, nausea, lack of appetite, pin sensation in her chest, and marked general weakness.

History taking was hardly possible due to cognitive deterioration. According to the patient, her highest blood pressure (BP) was 140/100 mm Hg. From 2010 the patient suffered from perceptive hearing loss, chronic pyelonephritis. From September 2018 — chronic hypochromic anemia (Hb: 96 g/L), diagnostic cancer search was undertaken. In 2019, the patient was hospitalised with tetraparesis, suspected acute cerebrovascular event (ACE);

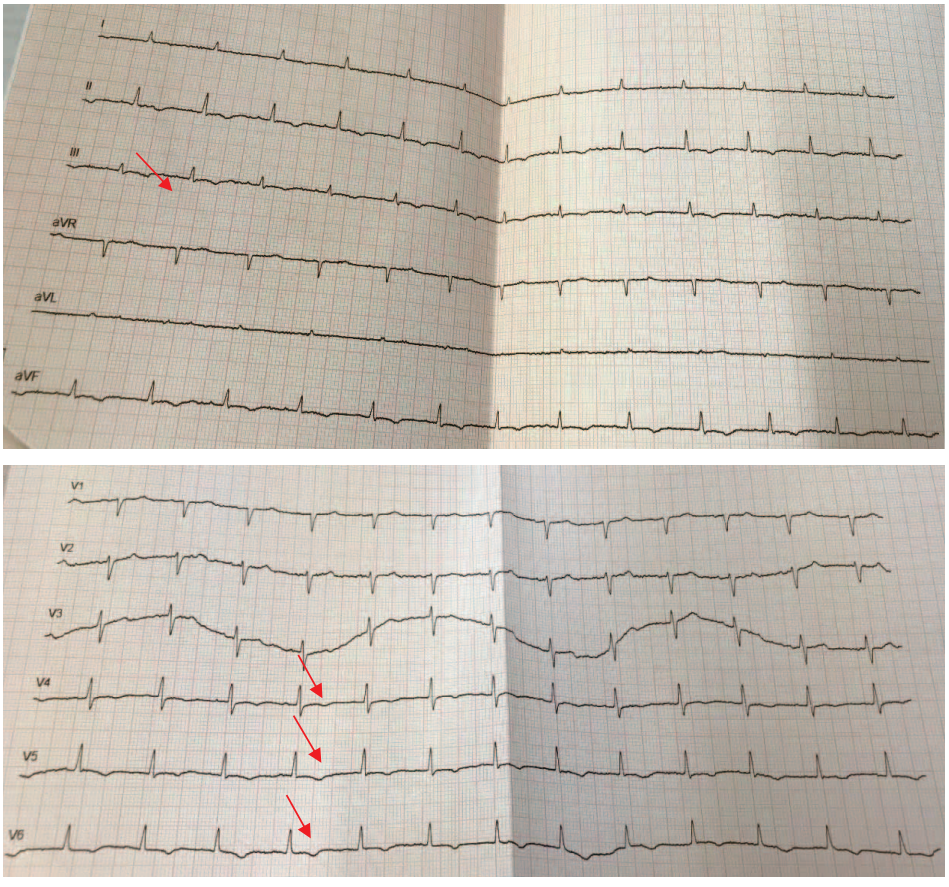


Figure. *1. Electrocardiogram of the patient with hypothyroidism: sinus rhythm, heart rate 80 per minute, normal heart axis, negative T waves in the apical, lateral and inferior walls of the left ventricle. The arrows indicate negative T waves in the respective leads*

Table 1. Hystory of symptoms of hypothyroidism, hiding behind various "masks"

Anamnesis of the disease of the patient Y.

2010	September 2018	September-November 2019	December 2019 February 2020	March 2020	September 2020
Bilateral sensorineural hearing loss, Chronic pyelonephritis	Severe general weakness, increased fatigue, hypochromic anemia (hemoglobin — 96 g/L)	Clinic of tetraparesis, acute dynamic intestinal obstruction (surgical treatment), anemia (hemoglobin 93 g/L)	The increase in edema of the lower extremities, an increase in the abdomen in size	Clinic of adhesive intestinal obstruction (conservative treatment), anemia (hemoglobin 80 g/L)	***Dynamic intestinal obstruction, stool retention, anasarca***

the diagnosis was not confirmed. During hospitalisation, the patient developed symptoms of acute dynamic bowel obstruction; laparotomy was required. The post-surgery period was complicated with staphylomycosis. After discharge from the hospital, the patient had gradually progressing lower limb edema, and her abdomen increased in size. In March 2020, the patient was re-admitted to the surgery department for the symptoms of adhesive bowel obstruction. After conservative treatment, the patient was discharged with improvements. According to the patient, she's feeling unwell due to a psychological stress, following wich she noticed stool retention for 5 days. The patient took laxatives and had loose stool for 4 days; her weakness progressed, and stabbing pain appeared in her abdomen and left chest. The electrocardiogram (Fig. 1) recorded by the ambulance team showed negative T waves in leads II, III, aVF, V4-V6. The patient was hospitalised to the cardiac intensive care unit with suspected acute coronary syndrome (ACS). Upon admission, the patient did not have any anginal pain; two troponin tests were negative; ECG did not show any negative dynamics. An abdomen and retroperitoneal space ultrasound (US) showed diffusive changes in liver and pancreas, free fluid in all sections of abdomen; in morison's pouch, the layer was up to 8 mm; kidneys: right kidney — 86*45 mm, left kidney — 99*44 mm; normal parenchymal echogenicity; the renal collecting system is indurated, not dilated; parenchymatous tissue is 15 mm thick. For diagnostic search and further management, the patient was transferred to the therapeutics department (Table 1).

Gynecologic history: two uncomplicated pregnancies and two deliveries. The patient denies smoking, alcohol consumption, narcotic and psychotropic substances.

Physical examination upon admission to the therapeutics department

Acute patient. Clear consciousness. Active position. Meningeal signs are negative. No focal neurologic symptoms. Slow speech. The patient is drowsy.

The skin has icteric discoloration, warm, not dry. Alopecia. Generalized edema of subcutaneous fat, including anterior abdominal wall, face, eyelids. Body temperature: 36.4^{0}C. The midline of anterior abdominal wall with a laparotomy scar, which healed with secondary adhesion.

Mixed shortness of breath was observed. The chest is evenly engaged in respiration. Percussion sound is clear and comes from lungs. Respiration is harsh, weak in inferolateral sections. No stridor. Respiratory rate (RR): 20/minute.

Region of the heart: unremarkable. Cardiac borders: unremarkable. The pulse is rhythmic, 66 bpm, not tense. The cardiac rhythm is regular. Muffled heart tones. No heart murmurs. Blood pressure: 90/60 mm Hg on both arms. Saturation (Sp O_2) — 94 %.

The tongue is pink, moist, with white coat. The abdomen is symmetric, enlarged due to non-tense ascites, moderately inflated, soft, sensitive to palpation in all sections. On palpation, liver is within the costal arch. Spleen is not palpable. Gall bladder is not palpable. Peristalsis is weak. Peritoneal signs are negative.

Kidney punch is negative on both sides. Urination is normal.

Clinical blood analysis: hyperskeocytosis up to 23.59 × 10^9/L, myelocytes: 3 %, stabs: 17 %, segmented cells: 71 %; lymphocyte depletion: 4 %.

Blood biochemistry shows hyperglycemia up to 7.1 mmol/L; hypercholesterolemia up to 6.0 mmol/L;

urea up to 9.7 mmol/L: ALT 23 U/L; AST 38 U/L; LDH 446 U/L; hyperbilirubinemia: total bilirubin up to 33.6 μmol/L, direct bilirubin 10 μmol/L; creatine phosphokinase increase up to 736 U/L; MB fraction 53.8 U/L, brain natriuretic peptide (BNP) 5 pg/mL, ALP 63 EU/L, total protein 67 g/L, albumin 36 g/L, potassium 4.37 mmol/L, hyponatremia up to 117 mmol/L; hypochloremia up to 93 mmol/L, C-reactive protein 5.86 mg/L, procalcitonin 1.8 ng/mL with dynamic reduction to 0.48 ng/mL, Fe reduction to 5.4 mmol/L.

Urinalysis: proteinuria 1 g/L, leukocyturia 92 per HPF, bacteriuria 18,623 (CFU/mL). Nechiporenko's test demonstrated an increase in WBC 13,500/mL, casts 9000/mL.

Echocardiography revealed enduration of aortic walls, aortal and mitral cusps. Cardiac chambers are not enlarged. Left ventricle (LV) myocardial hypertrophy. No regional contractility abnormalities were found. LV ejection fraction (Simpson's EF) is 56 %. Stage 1 mitral regurgitation, stage 1 tricuspid regurgitation. Mild cardiac dropsy — pericardial layer separation is up to 4 mm behind posterior LV wall (Fig. 2).

Chest CT native-phase images do not show any focal or infiltrative changes. Signs of dropsy of chest, abdominal dropsy.

Abdominal contrast CT: signs of colitis, abdominal dropsy, bilateral dropsy of chest (right: up to 500 cm^3; left: up to 250 cm^3), signs of lung parenchyma compression in the right lower lobe. Comparison with CT scans taken seven months ago shows negative dynamics: generalized edema, progressing colon edema. Significant diffusive colon wall edema is marked with arrows (Figure 3).

Preliminary diagnosis:

Tubulointerstitial bacterial inflammatory kidney disease. Toxic syndrome. Systemic inflammatory response syndrome. Chronic kidney disease C3a (CKD-EPI e-GFR: 51.46 mL/min/1.73 m^2), A2. Chronic moderate hypochromic anemia. Stage 3 arterial hypertension, uncontrolled AH. Edematic-ascitic syndrome: bilateral dropsy of chest, cardiac dropsy, abdominal dropsy. Fluid and electrolyte disorder syndrome/ Dyslipidemia. Extremely high cardiovascular risk. Chronic cerebral ischemia. Perceptive hearing loss. NAFLD: non-alcoholic fatty liver disease with moderate laboratory activity. Peritoneal commissures. Chronic colitis, acute stage.

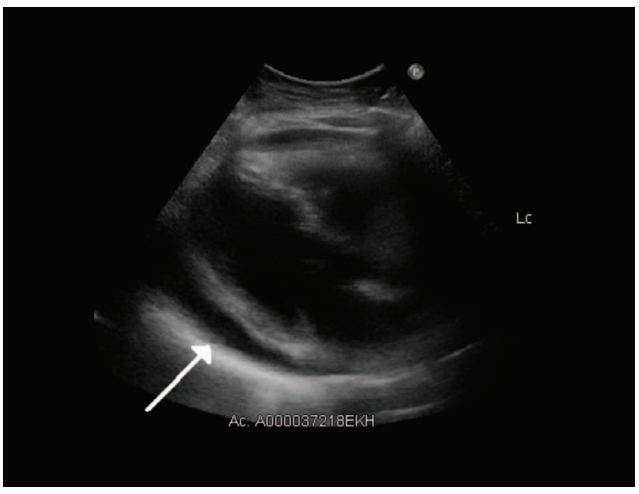


Figure 2. *Echocardiogramm of the patient with hypothyroidism. Fluid (indicated by an arrow) in the pericardial cavity, divergence of the pericardial sheets along the posterior wall up to 4 mm*

Taking into account alopecia, edema syndrome with normal systolic LV fraction and normal BNP, slow speech and movements, thyroid gland pathology with deficiency was suspected. Hypothyroidism was confirmed with laboratory tests: TTH 32.6 μU/mL; free T4 < 1 pmol/L; total T3 < 40 nmol/L; anti-TPO < 10 U/mL. Thyroid gland ultrasound revealed significantly reduced gland size which was 1.6 cm^3 (normal values for women: 4.0–18.0 cm^3). Gland echogenicity and structure, blood supply, regional lymph nodes are normal.

During hospitalisation, the patient underwent the following complex treatment:

- T. Levothyroxini 100 μg once daily per os as hormone replacement therapy, taking into account hypothyroidism severity established by laboratory tests and instrumental assessments.
- S. Cefoperazoni + Sulbactami 1 g + 1 g twice daily by intravenous infusion for an acute episode of chronic pyelonephritis.
- S. Furosemidi 40 mg 2 tablets once daily, and T. Spironolactoni 50 mg daily per os for edematic-ascitic syndrome.
- T. Omeprazoli 20 mg 1 capsule twice daily per os for gastric protection.
- S. Natrii chloridi 0.9 % 500 mL; S. Trisoli 400.0 mL once daily by intravenous infusion for water-electrolyte disorder correction.
- S. Metoclopramidi 10 mg 2 ml IM as as pro-kinetic.
- S. Platiphyllini 4 mg 2 mL IM as an antispastic drug.

Despite the therapy, on hospitalisation day 12 the patient experienced circulatory arrest. ECG monitor readings: electromechanical dissociation with HR 8–10/minute with subsequent asystole; resuscitation procedure was ineffective, and the patient was pronounced dead.

Postmortem: underlying disease — primary hypothyroidism, probably caused by Hashimoto's thyroiditis (antibody-free variant), newly diagnosed.

Complications: internal organs dystrophia. Generalized edema: cardiac dropsy (100 mL), bilateral dropsy of chest (right: 1500 mL, left: 800 mL); abdominal dropsy (2000 mL); edema of extremities, face, trunk, lungs, brain. Focal bronchial pneumonia in lower lobe of the left lung.

Anemia (Hb: 109 g/L). Proteinuria (urine protein: 1.0 g/L). Chronic fibrinous colitis, acute phase.

Comborbidities: arterial hypertension (heart mass: 320 g, LV myocardium thickness: 1.7 cm). Atherosclerosis of aorta (stage 4, 2nd degree). Atherosclerotic cardiosclerosis, atherosclerosis of aorta and coronary arteries (stage 3, 2nd degree, stenosis up to 25 %). Sequellae of acute cerebrovascular event: a brown cyst in left basal nuclei, cerebral atherosclerotic vascular disease (stage 1, 2nd degree). Dense abdominal fibrous adhesions. Laparotomy for acute dynamic bowel obstruction in 2019.

It is interesting that during postmortem examination, when the organs were removed from the body, thyroid gland was not found either by visual inspection

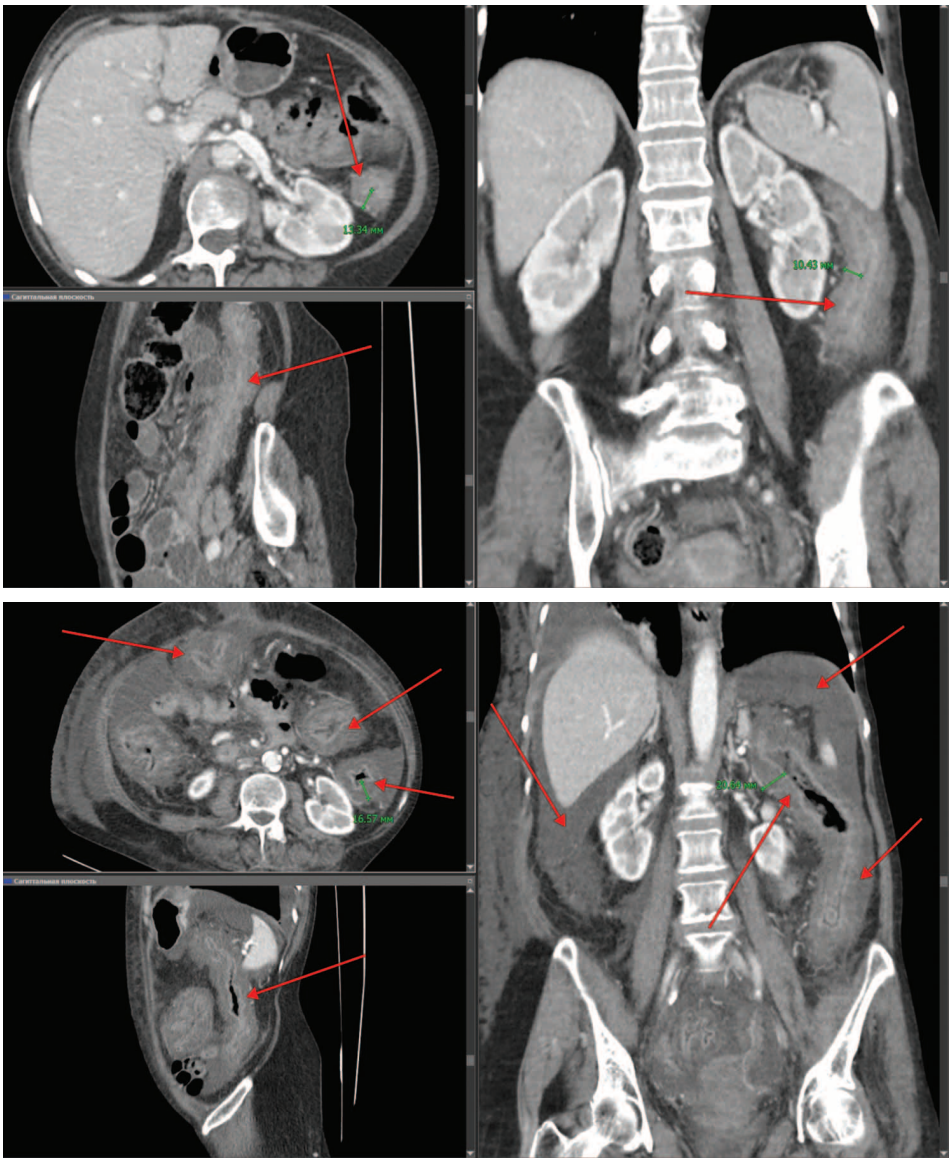
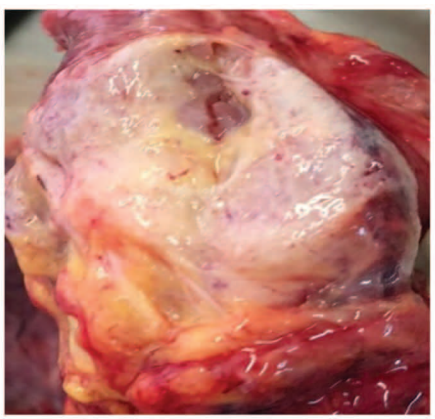
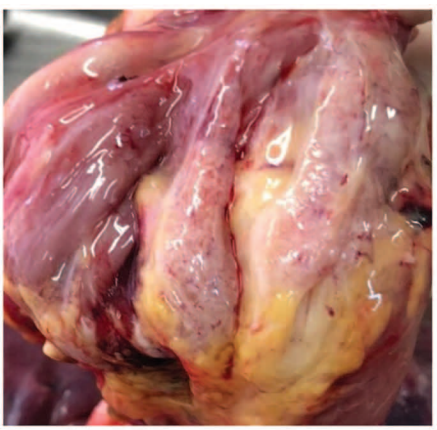


Figure 3. *Multislice computed tomography (MSCT): edema of the colon wall throughout (indicated by arrows)*



а) Правая доля щитовидной железы



б) Левая доля щитовидной железы

Figure 4. *Atrophy of the right and left lobe of the thyroid gland. macropreparation. Magnification 1×1000*

or on palpation. A series of sections in the anatomic localisation area of the right lobe showed a pale pink band (3.2×1.0×0.7 cm) (Figure 4a); a similar band was observed in the anatomic localisation area of the left lobe (3.9×0.7×0.9 cm) (Figure 4b); a macroscopic examination did not visualise the isthmus of gland.

Histologic examination of the right lobe demonstrated fibrous hyalinized connective tissue with marked edema, focal lymphocytic infiltration and single plasma cells; isolated follicles from large Hurthle cells with oxyphilic cytoplasm and central basophilic nucleus, numerous thin-wall full-blooded vessels (Figure 5).

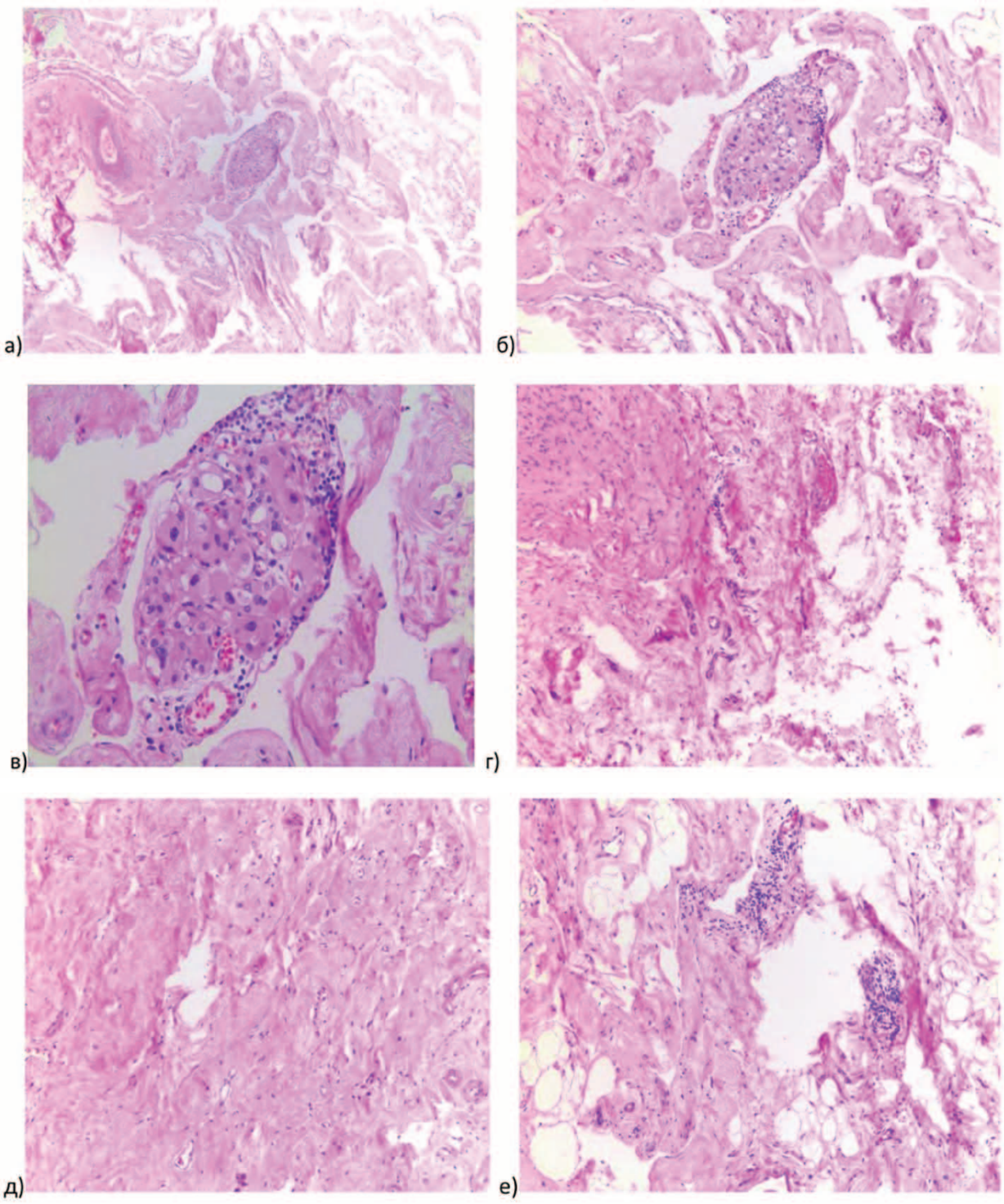


Figure 5. *Tissue of the right lobe of the thyroid gland: fields of fibrous hyalinized connective tissue with severe edema, focal lymphocytic infiltration and single plasma cells (а, б, г, д, е), single follicles of large Ashkinazi-Gurtl cells with oxyphilic cytoplasm and a centrally located basophilic nucleus (в), many thin-walled full-blooded vessels (б, в, д, е)*
Staining with hematoxylin and eosin, а) magnification ×50, б) magnification ×100, в) magnification × 200, г) magnification ×100, д) magnification ×100, е) magnification ×100

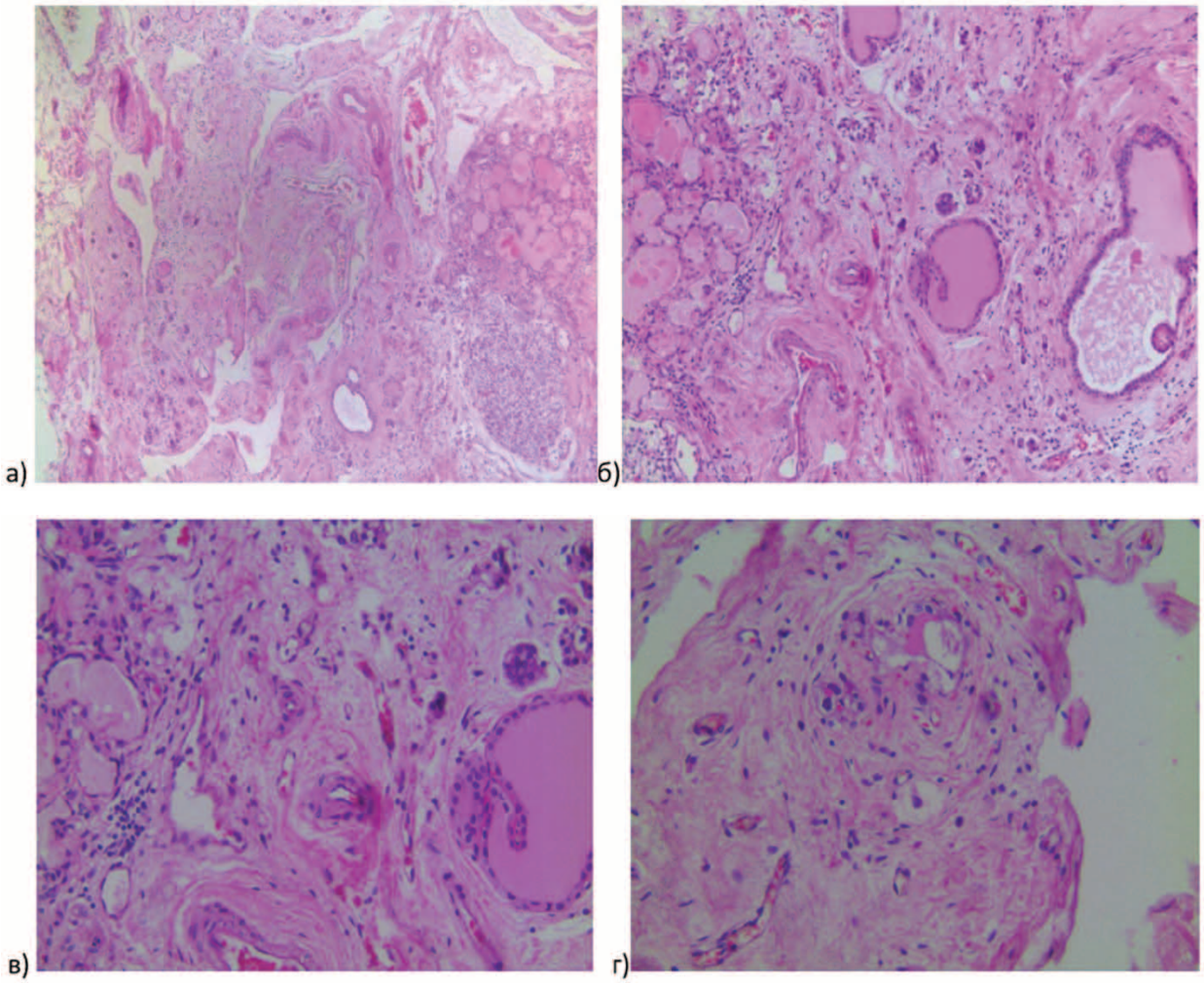


Figure 6. *Fields of fibrous connective tissue with pronounced edema, focal lymphocytic infiltration and single plasma cells, in one of the preparations, lymphocytic infiltration is represented by a lymphoid follicle (а); among the fibrous stroma, there are islands of gland tissue represented by follicles of various sizes, partially filled with colloid (а, б, в, г), in single follicles papillary growths (б, в) of the tissue of the left lobe of the thyroid gland: Staining with hematoxylin and eosin, а) ×50 magnification , б) magnification ×100, в) magnification ×200, г) magnification ×200*

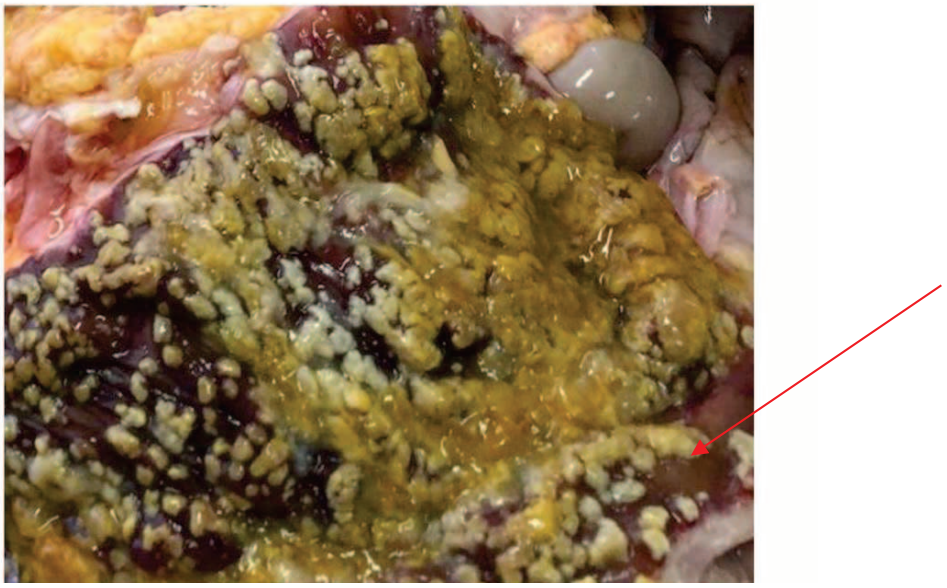


Figure 7. *Macropreparation of the large intestine. The arrow indicates the imposition of fibrin*

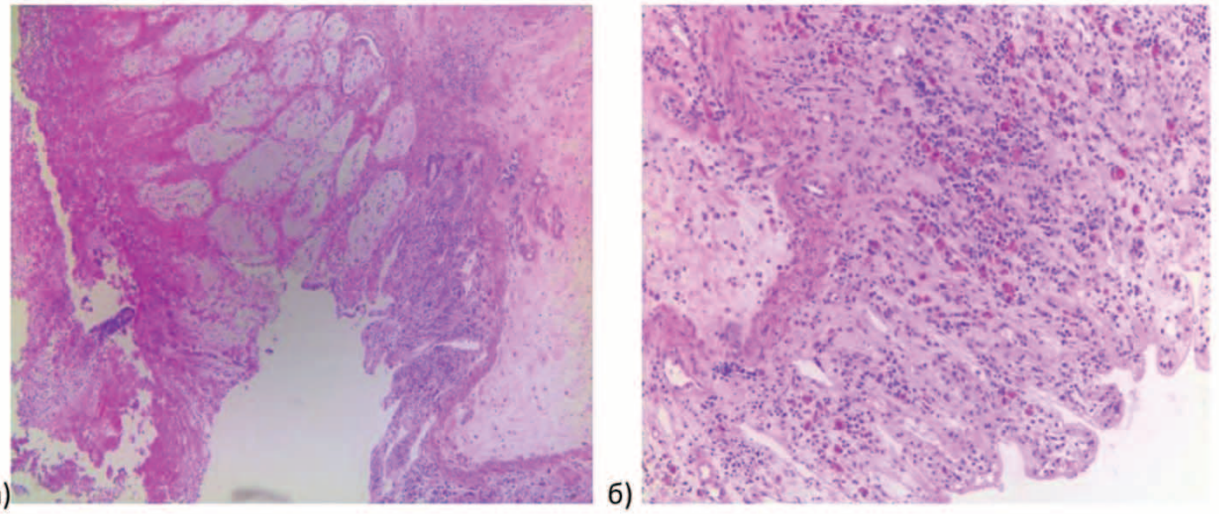


Figure 8. *Shortening and atrophy of the crypts of the mucous wall of the colon. In some areas, necrosis of the superficial sections of the crypts covered with fibrin (a). Mucosa and submucosa with severe edema and severe infiltration of lymphocytes and plasmocytes, single eosinophils and macrophages loaded with hemosiderin (б). Sclerosis of the lamina propria. In the submucosa there are full-blooded dilated vessels, the muscular membrane with moderate edema. Hematoxylin and eosin staining, a) ×50 magnification, б) ×100 magnification*

Histologic examination of the left lobe (Figure 6) revealed fibrous connective tissue with marked edema, focal lymphocytic infiltration, and isolated plasma cells; in one sample, lymphocytic infiltration is represented by a lymphoid follicle; fibrous stroma has gland tissue inlets represented by follicles of various sizes, partially filled with colloidal matter; follicles contain papillary projections.

Macroscopic examination: colon serosa is greyish-pink, smooth, glossy. The wall is edematic, indurated. Mucosa is cherry red with numerous fibrin overlaps and oval mucous defects (0.2×0.1×0.1 cm to 0.3×0.2×0.1 cm); the bed of the defects is red (Figure 7).

Pathomorphological study: the intestine wall shows shorter atrophic crypts. Necrosis of cryps surface areas covered with fibrin. Mucosa and submucosa are markedly edematic, with significant lymphocytic and plasmocytic infiltration, isolated eosinophils and hemosiderin-laden macrophages. Sclerosis of lamina propria. Submucosa contains full-blooded enlarged vessels; the muscular layer is moderately edematic (Figure 8).

Discussion and conclusion

The authors present a case study of a 60-year-old patient with severe hypothyroidism associated with chronic Hashimoto's thyroiditis. Hypothyroidism was not diagnosed until two years after manifestation of symptoms of a severe disease with almost all typical signs and symptoms of the disease. By the time when the diagnosis was made, the patient had symptoms of severe hypothyroidism, such as atony, adynamia, drowsiness, alopecia, depression, intellectual deterioration, hypotony, generalized edema with abdominal dropsy, dropsy of chest, cardiac dropsy, history of transient tetraplegia, dynamic bowel obstruction, and marked water-electrolyte disorders (hyponatremia, hypochloremia), dyslipidemia. Unfortunately, despite hormone replacement therapy, the patient's condition could not be compensated, and the patient died.

This case study is a good example of challenges with assessment of the seemingly typical symptoms of primary hypothyroidism and their interpretation as the signs of completely different somatic and psychoneurological disorders.

Though seemingly straightforward, hypothyroidism diagnosis has its own issues. First, by the time of the last hospitalisation the patient had a number of complications and conditions associated with hypothyroidism, that were concealing the clinical manifestations. Second, postmortem examination verified disease sequellae in the form of ACE, that might also have contributed to the development of intellectual and mnestic disorders. Third, the patient did not present with increased anti-TPO titer at the late stages of chronic Hashimoto's thyroiditis.

Therefore, when facing symptoms resembling hypothyroidism in the real clinical practice, including edematic-ascitic syndrome, anemia, bowel obstruction of unknown etiology, any medical professional should include hypothyroidism into differential diagnosis, in order to timely test serum TTH levels and start replacement therapy before severe complications develop.

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МИКРОСКОПИЧЕСКИЙ КОЛИТ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Microscopic Colitis: A Clinical Case

Резюме

Микроскопический колит — это воспалительное заболевание кишечника неизвестной этиологии, проявляющееся в виде хронической диареи водянистого характера, с отсутствием эндоскопических признаков поражения кишечника, но наличием микроскопических изменений. Диагностика микроскопического колита основывается на гистологическом исследовании биоптата кишечника и требует высокой квалификации гастроэнтеролога, эндоскописта и гистолога. В статье представлен клинический случай микроскопического колита у пациентки 42 лет, обсуждаются основные этапы дифференциальной диагностики и лечения.

Ключевые слова: *микроскопический колит, будесонид, коллагенозный колит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Microscopic colitis is an inflammatory bowel disease of unknown etiology that presents as chronic watery diarrhea with no endoscopic evidence of the bowel involvement but with the microscopic changes. Diagnosis of microscopic colitis is based on the histological examination of the intestinal biopsy and requires a highly qualified gastroenterologist, endoscopist and histologist. The article presents a clinical case of microscopic colitis in a 42-year-old patient, reflects the main stages of diagnosis and treatment of the patient.

Key words: *microscopic colitis, budesonide, collagenous colitis*

Conflict of interests

The authors declare no conflict of interests

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MC — microscopic colitis, CC — collagenous colitis, LC — lymphocytic colitis, IRS — irritable bowel syndrome, GCS — glucocorticosteroids, PPI — proton pump inhibitors

Microscopic colitis (MC) is an inflammatory bowel disease of unknown etiology, manifested as chronic watery diarrhea with no endoscopic signs of bowel involvement but with microscopic changes [1]. MC is classified into two types: collagenous colitis (CC) and lymphocytic colitis (LC). The prevalence of MC is 103.0 per 100,000 population: 39.3 per 100,000 population for CC and 66.7 per 100,000 population for LC. According to the Guidelines of the United European Gastroenterology (UEG) and European Microscopic Colitis Group (EMCG), 2021, sometimes a third type of MC (incomplete MC) is used. Diagnosis of MC is based on the histology of the bowel biopsy specimen and requires participation of a qualified gastroenterologist, endoscopy specialist and histologist. MC type is determined based on the morphological data. Different types have similar clinical presentation [2].

The prevalence of MC is higher in the elderly, median patient age in CC and LC is 64.9 and 62.2 years, respectively. Although recent studies have showed that up to 25 % of patients diagnosed with CC were younger than 45 years. Also, there were cases of CC in children and adolescents [3].

Etiology and pathogenesis of the MC are not fully studied. The literature discusses various mechanisms and risk factors potentially associated with MC, including genetic predisposition, impaired epithelial permeability, infectious and immunologic factors, impaired collagen metabolism (for CK), malabsorption of bile acids [2].

Most authors stand for the immune-mediated nature of MC, with a significant contribution of both the immune system and cytotoxic reactions. The inflammatory cascade is most likely to trigger exposure to certain intraluminal bacterial antigens that enter the lamina propria of the intestinal mucosa, as well as drug products that increase mucosal permeability. Genetic factors affect the processes of antigen presentation by immunocompetent cells in the intestinal mucosa, which leads to hyperactivation of the Th1- and Th17-type immune response and to the development of cytotoxic effects with subsequent injury to the epithelium. Elevated mucosal concentrations of profibrogenic cytokines such as transforming growth factor β, interleukins 6 and 22 appear to be highly associated with CC rather than with other forms of MC and are likely to mediate subepithelial collagen deposition, which is a distinctive histologic sign of CC [2, 4].

Below is a clinical case demonstrating the challenges of diagnosis in a patient with MC.

In January, 2021 a 42-year-old female patient visited a gastroenterologist at the ON CLINIC International Medical Center with complaints of loose, watery stool (type 6 according to the Bristol Stool Chart) up to 6 times a day, sudden uncontrollable urge to defecate, bloating accompanied by moderate pain. Historical data suggest that these signs have persisted for 4 years. The patient has no previously diagnosed chronic diseases. Over this period, repeated examinations were carried out, including abdominal ultrasound, clinical and biochemical blood tests, coprological examination, stool tests for microbiocenosis, for protozoa and helminth eggs. Test results were normal. Thyroid panel (thyroid stimulating hormone, triiodothyronine and thyroxine) is within normal range. One year before admission, a fiberoptic colonoscopy was carried out, which did not reveal any abnormalities in the large bowel. Celiac disease, lactase insufficiency, chronic pancreatitis and bacterial overgrowth syndrome have been ruled out. The patient underwent a number of cycles of therapy with various spasmolytics, enzyme products, prebiotics, probiotics, antidiarrheic products with no effect. The patient had to take loperamide chronically and use diapers.

The patient has no allergies or bad habits. Her father was diagnosed with the rectal cancer at the age of 70 years. From the mother's side family history is not burdened.

Physical examination: skin and visible mucous membranes were of normal color. Height: 177 cm, bodyweight 58 kg (body mass index 18.5 kg/m^2). The tongue was moist, covered with white fur. The abdomen was of regular shape, soft, moderately bloated, tender on superficial palpation in the epigastric area. Deep sliding palpation according to Obrazcov — Strazhesko showed no abnormalities.

According to the above data, the patient was diagnosed with the irritable bowel syndrome (IBS). Recommendations: fractional meals 5–6 times a day, excluding fatty, fried, spicy, smoked, pickled food and alcohol; a 10-day course of medical therapy: alverine + simethicone 1 capsule TID, smectite dioctaedric 1 sachet TID,

pancreatin in minimicrospheres 10,000 units 1 capsule TID, natural lyophilized homogenized avian gastric mucosa 300 mg TID (it has a cholinolytic, adsorbing and coating effect), as well as the biologically active compound calcium butyrate + inulin 1.36 g, 2–3 times a day for up to 3 months.

Laboratory tests: hematology showed an increase in ESR to 29 mm/h (hereinafter, normal range is indicated in parentheses: 1–20 mm/h), hemoglobin 120 g/l (120–140 g/L), white blood cells 5.15×10^9/L ($4.0–9.0\times10^9$/L). Stool is liquid, unformed, with single WBCs per HPF, and total lack of neutral fat and fatty acids. Slight reduction in typical Escherichia coli titer to 10^5 CFU/g (ref. range: $10^7–10^8$ CFU/g); Fecal calprotectin 2.8 mg/kg (0–50 mg/kg). To rule out intestinal infections, passive hemagglutination test to salmonella, shigella, yersinia was carried out with a negative result. To rule out parasitic invasions, tests for antibodies to ascaris, opisthorchis, *Entamoeba histolytica*, lamblia, toxocara, Fasciola hepatica were carried out. Anti-ascaris antibodies were identified: IgG 1.69 U (0–1.1 U). According to the abdominal ultrasound, gallbladder deformity was observed.

The patient was consulted by a mental health specialist. Psychoneurological state is normal.

After a repeated consultation of gastroenterologist after one month of treatment, the patient was followed up for IBS and diarrhea. It was recommended that the current chronic therapy should be supplemented with products containing Bifidobacterium adsorbed on activated carbon, 2 capsules once daily and Hylak forte 40–60 drops TID. Due to the increased titer of anti-Ascaris antibodies, it was decided to conduct antiparasitic therapy with mebendazole 100 mg BID for 3 days. At the repeated test after 6 weeks, anti-Ascaris antibodies were not detected. Diarrhea persisted.

At the repeated visit after 1 month there were no signs of clinical improvement. Due to the lack of therapeutic effect, colonoscopy with gradual biopsy was recommended for diagnostic purpose. According to fibrocolonoscopic data, the lumen of the cecum, ascending, transverse, descending and sigmoid colons was dilated by 2/3 of diameter. Intestinal mucosa was smooth, shiny, significantly thinned. The vascular patten was increased, not deformed. The sigmoid colon had an additional loop, significantly motile. Histology of the material sampled from four segments of the large bowel (ascending, transverse, descending colon and sigmoid) showed chronic erosive colitis with significant hyperplasia of the lymphoid follicles. Taking into account the clinical presentation that was not typical of erosive colitis, a decision was made to repeat histologic examination to rule out microscopic colitis. Medical therapy was started: 5-aminosalycilic acid (granulated, Mesalazine), 2000 mg/day.

Repeated histology of the endoscopy specimen showed the following: the colon mucosa showed changes of similar pattern (Figure 1): dystrophy, necrobiosis and large areas of desquamation of the superficial epithelial cells. A number of lymphocytes was noted between the epithelial cells (up to 20–25 per 100 epithelial cells), as well as single eosinophils. The subepithelial collagen layer thickness was increased, up to 20–30 μm in some areas (more in distal segments of the colon). The intestinal glands were shallow, with normal structure. The epithelial layer of the glands contained a large amount of goblet cells. The lamina propria was diffusely infiltrated with lymphocytes and plasmocytes with a significant admixture of eosinophils. Follicle-like aggregations of lymphocytes. Inflammatory infiltrative cells did not spread to the submucosa. According to the histologic data, MC in the form of CC was verified.

Therefore, taking into account the clinical signs, chronic watery diarrhea, moderate abdominal pain, lack of effect of enzyme preparations, probiotics and prebiotics, lack of significant abnormalities according to the instrumental data, as well as histological examination (increase in the thickness of the subepithelial collagen layer in separate areas up to 20–30 μm), collagenous MC

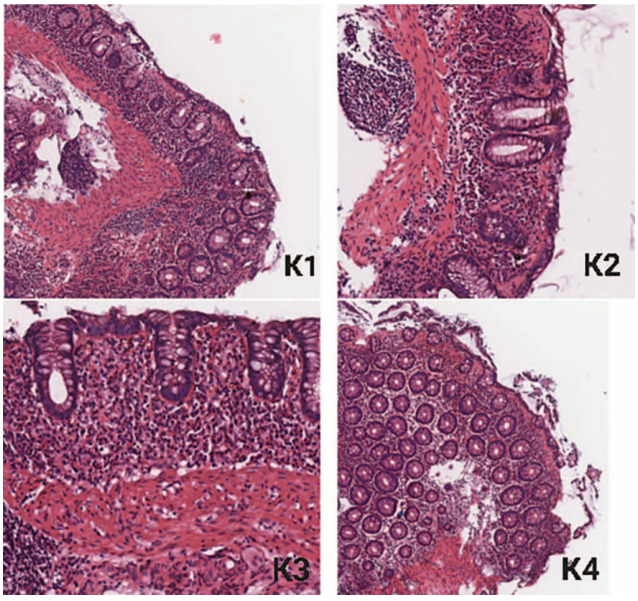

Figure 1. *Histological examination of endoscopic material from the ladder biopsy of the intestine (description in the text)*

Note: In the micropreparations shows fragments of the ascending (K1), transverse colon (K2), descending (K3) and sigmoid colon (K4). There is dystrophy, necrobiosis and extensive areas of desquamation of cells of the surface epithelium. The thickness of the layer of subepithelial collagen is increased, in some areas up to 20-30 microns

was diagnosed, continuously recurrent form, of moderate severity, which required prescription of a topical glucocorticosteroid (GCS) budesonide 9 mg per day.

Within two months after loading dose of GCS the patient noted normalization of stool, improvement of the general well-being, and stabilization of the emotional state. At the second visit after 6 months of treatment with GCS, there were no clinical signs of disease; the patient stopped using diapers. A decision was made to reduce a dose of budesonide to 6 mg/day with tapering of GCS. Currently the patient does not use GCS. After discontinuation, there were no signs of recurrence.

Discussion

In most cases MC is not life-threatening, but it affects quality of life. Therefore, timely diagnosis of the condition is an urgent problem [5].

MC has no specific syndromes or signs. MC can be suspected in the presence of the following conditions: watery diarrhea more than 3 times a day over a long time without blood admixture, infection and inflammation, complaints of fecal incontinence, patient's age >50 years, concomitant autoimmune diseases (e.g., Raynaud, Sjögren, rheumatoid arthritis, etc.), long-term use of cytostatics or monoclonal antibodies. The only method of diagnosis confirmation is fiberoptic colonoscopy with targeted biopsy and histologic examination. It is mandatory to perform sampling from all segments of the large bowel [2, 3].

MC treatment is aimed at reducing inflammation and diarrhea intensity. Treatment should be based on the use of GCSs: in the majority of cases, topical GCS (budesonide 9 mg/day) is recommended for three months. Due to the high frequency of relapses a number of experts consider it reasonable to continue budesonide at a dose of 6 mg/day up to 3 months followed by its use at a dose of 3 mg/day up to 6 months [3, 5].

It should be noted that MC is a diagnosis of exclusion, which requires a highly thorough examination and histologic examination by an experienced morphologist. Unfortunately, if MC is not verified, therapy is inadequate. Most commonly IBS is masked by MC, which leads to a prolonged lack of the appropriate therapy. The main differences between MC and IBS are age (most often, young age in IBS and old age in MC) and the character of stool (2–4 times/day, not abundant, unformed in IBS, 4–5 times/day, abundant, loose in MC). Malabsorption and weight loss, as well as comorbid with autoimmune condition, are not uncommon (Table 1). Histologic examination of the intestinal mucosa is the gold standard in the diagnosis of MC [2, 3, 5].

Taking into account the above data, it is important to apply the algorithm of diagnosis and examination of such patients to identify such rare condition as MC. It is necessary to develop domestic algorithms for routing patients with CM like in other chronic diseases [6].

The biomedical research database Pubmed contains 78 publications on the query "microscopic colitis clinical case" over the past 5 years (135 cases over 10 years). Although it should be noted that only 27 articles specifically described microscopic colitis; in other publications this condition is discussed with regard to differential diagnosis. Russian Science Citation Index (RSCI) contains information on only two clinical cases: lymphocytic and incomplete variants of microscopic colitis in women over 50 years of age [7, 8].

When comparing the published data with the presented clinical observation, the relatively young age of the patient (42 years) is noteworthy, while most described cases of microscopic colitis occur in patients older than 50 years.

A rather large number of clinical situations is associated with the use of drug products. Therefore, Monjur Ahmed and Gloria Francis (2018) described a clinical case of pembrolizumab-induced microscopic colitis. A 54-year-old patient received pembrolizumab for squamous cell nasopharyngeal carcinoma. After a long-term treatment period, persistent diarrhea developed within 3 weeks. Instrumental and laboratory data did not show organic abnormalities. Therefore, a decision was made to conduct gradual biopsy of the large bowel. Based on the results, LC was diagnosed. Pembrolizumab is

Table 1. *Clinical differences between irritable bowel syndrome and microscopic colitis*

	Irritable bowel syndrome	Microscopic colitis
Patient's age	In most cases under 50 years of age	In most cases over 50 years of age
Character of stool	2-4 times a day sparse, unformed	4-5 times a day, plentiful, liquid
Fecal incontinence	Rarely	Often
Maladsorption syndrome and weight loss	Rarely	Often
Comorbidity with autoimmune diseases	Rarely	Often
Comorbidity with psychosomatic diseases, stress	Often	Rarely

a G4 humanized immunoglobulin, which, in turn, may trigger autoimmune reaction in the form of MC [9].

Early publications describe some clinical cases associated with the use of proton pump inhibitors (PPI). Gilbert M. et al. (2009) described 4 clinical cases of MC during treatment with PPI. Long-term therapy with PPI was prescribed to the patients with peptic ulcer or gastroesophageal reflux. After long-term treatment with these products, persistent diarrhea with an unknown cause developed in 4 patients. Only after biopsy MC was diagnosed, after which budesonide was prescribed, and diarrhea resolved [10].

In the majority of the analyzed cases patients had extensive comorbidities, including various autoimmune conditions.

In the described clinical case, the patient did not receive any drug products that may cause MC. The patient had no comorbidities either. Although clinical course of the MC in a patient was similar to that described in literature. The only specific syndrome typical of MC in this patient was persistent watery diarrhea resistant to the symptomatic therapy. This underlines the importance of the thorough history taking and appropriate assessment of the clinical signs within the patient-oriented approach.

According to the literature, the treatment is based on the use of topical GCS (budesonide), although in a large number of patients it did not lead to a strong remission [2]. In this case, a rapid favorable effect of treatment was noted followed by a strong remission.

Conclusion

Therefore, histologic pattern plays a major role in the diagnosis of MC. In cases of diarrhea of unclear etiology and lack of visible changes on colonoscopy, a gradual biopsy is necessary to verify diagnosis. After accurate diagnosis, treatment with GCS is indicated to reduce the severity of clinical signs of MC and improve prognosis.

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