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АУТОИММУННЫЙ/ВОСПАЛИТЕЛЬНЫЙ СИНДРОМ, ИНДУЦИРОВАННЫЙ АДЪЮВАНТАМИ

A.A. Zayaeva, S.I. R. Younsi*, A.I. Zausalina, G.N. Koshukova, A.V. Klimchuk, G.A. Younsi

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Autoimmune/Inflammatory Syndrome Induced by Adjuvants

Резюме

ASIA-синдром (autoimmune/inflammatory syndrome induced by adjuvants –аутоиммунный/воспалительный синдром, обусловленный адъювантами, синдром Шонфельда (Shoenfeld's syndrome)) представляет собой группу аутоиммунных заболеваний, вызванных адъювантами, обладающими способностью индуцировать иммунные реакции. Синдром включает пять иммуноопосредованных состояний, которые связаны с предшествующим воздействием различных триггерных факторов, такие как силиконоз, синдром макрофагального миофасцита, синдром Персидского залива, синдром «больных» зданий и поствакцинальные аутоиммунные явления. Развитие ASIA-синдрома связано с индивидуальной генетической предрасположенностью и возникает в результате сочетанного воздействия экзогенных и эндогенных факторов, запускающих аутоиммунный ответ. При этом, реакция иммунной системы может быть непредсказуемой. В статье приведены диагностические критерии синдрома, а также его клинико-лабораторные и морфологические проявления. Спектр клинических проявлений аутоиммунного/воспалительного синдрома, индуцированного адъювантами, обширен и затрагивает практически все системы организма человека. При этом, его характерным признаком является регресс клинических, лабораторных и морфологических проявлений после удаления адъюванта. Нет сомнений в том, что ASIA-синдром прояснил роль адъювантов в развитии аутоиммунных процессов. Это должно учитываться при создании безопасных вакцин, силиконовых имплантов, филлеров и других медицинских изделий с минимальными побочными эффектами. Кроме того, медицинские работники должны повышать уровень осведомленности пациентов о побочных эффектах применения некоторых косметологических процедур и использования силиконовых имплантов, для чего необходимо включить в учебно — методические пособия для студентов, ординаторов и врачей различных специальностей описание этиологии, патогенеза, диагностики и лечения ASIA — синдрома, как отдельной нозологической единицы.

Ключевые слова: **аутоиммунный/воспалительный синдром, индуцированный адъювантами, ASIA — синдром, синдром Шонфельда, адьювант**

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Abstract

ASIA syndrome (autoimmune/inflammatory syndrome induced by adjuvants) is a group of autoimmune diseases caused by adjuvants that have the ability to induce immune responses. The syndrome includes five immune-mediated conditions that are associated with prior exposure to various trigger factors, such as siliconosis, macrophage myofasciitis syndrome, Persian Gulf syndrome, sick building syndrome, and post-vaccination autoimmune events. The development of ASIA syndrome is associated with an individual genetic predisposition and occurs as a result of the combined effect of exogenous and endogenous factors that trigger an autoimmune response. In this case, the reaction of the immune system can be unpredictable. The article presents the diagnostic criteria for the syndrome, as well as its clinical, laboratory and morphological manifestations. The spectrum of clinical manifestations of the autoimmune/inflammatory syndrome induced by adjuvants is extensive and affects almost all systems of the human body. At the same time, its characteristic feature is the regression of clinical, laboratory and morphological manifestations after removal of the adjuvant. There is no doubt that ASIA syndrome has clarified the role of adjuvants in the development of autoimmune processes. This should be taken into account when creating safe vaccines, silicone implants, fillers and other medical devices with minimal side effects. In addition, medical professionals should raise patients' awareness of the side effects of using certain cosmetic procedures and the use of silicone implants, for which it is necessary to include a description of the etiology, pathogenesis, diagnosis and treatment of ASIA syndrome in teaching aids for students, residents and doctors of various specialties as a separate nosological unit.

Key words: *autoimmune/inflammatory syndrome induced by adjuvants, ASIA syndrome, Schoenfeld's syndrome, adjuvant*

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ASIA-syndrome — autoimmune/inflammatory syndrome induced by adjuvants; MHC — Major Histocompatibility Complex; HLA DRB1 — Human Leukocyte Antigens, class II, beta chain; HBV — Hepatis B virus; HPV – Human papillomavirus; HAV — Hepatis A virus; HLA-B27 — Human Leukocyte Antigens, class I, beta chain; PTPN22 — Protein tyrosine phosphatase non-receptor type 22.

Introduction

ASIA-syndrome (autoimmune/inflammatory syndrome induced by adjuvants, Shoenfeld's syndrome) is a group of autoimmune diseases, such as silicosis, macrophage myofascitis syndrome, Persian Gulf syndrome, sick building syndrome and post-vaccination autoimme conditions induced by adjuvants (Figure 1). Identification of ASIA-syndrome made it possible for the first time to group specific conditions caused by hyperergic immune reaction to various adjuvants.

Adjuvants are substances that boost immune response when administered together with an immunogen [1]. They have immunomodulating action [2]. Usually adjuvants can be found in drugs, vaccines, silicone breast implants, mineral oils and cosmetics. Despite the fact that adjuvants are predominantly safe, sometimes administration of adjuvants can induce immune response in genetically susceptible and predisposed persons [1].

The scientific theory underlying Shoenfeld's syndrome is based on paradigms widely recognised in published studies. First of all, it is noted that genetic predisposition has a leading role in autoimmune process development. Numerous studies demonstrated the correlation between a certain genetic profile and autoimmune processes. Of all genetic loci defining predisposition to autoimmune reactions, most significant are

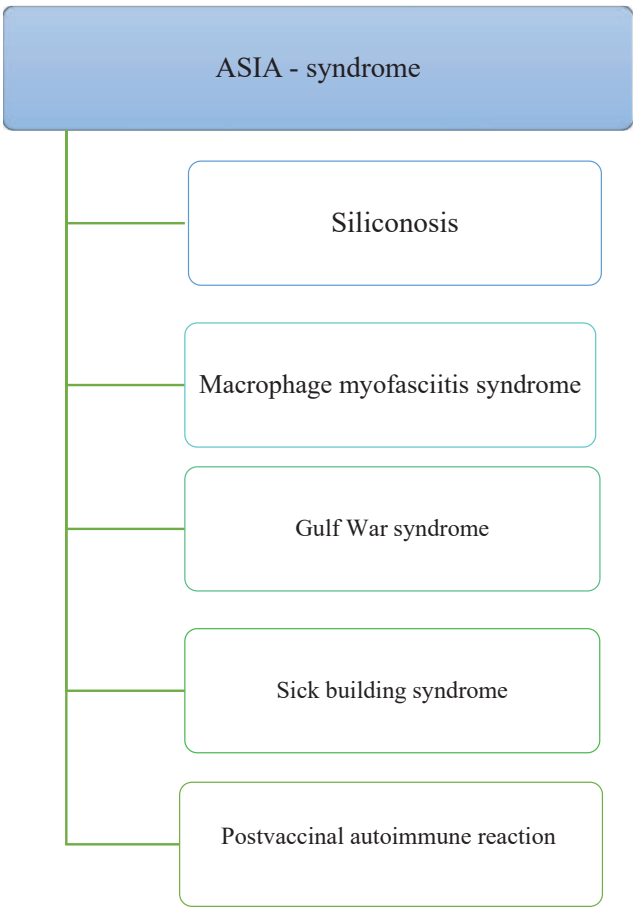

Figure 1. *Immune — mediated cjnditions ASIA syndrome*

the loci that encode type II MHC (major histocompatibility complex), responsible for antigen presentation to immune cells. However, the mechanism of MHC II involvement into autoimmune process has been understudied. It is likely that aberrant antigen presentation is a result of allele variants of the major histocompatibility complex, such as HLA DRB1 autologous-reactive T-lymphocytes [3]. It is assumed that genetic predisposition to an autoimmune process is associated with certain MHC alleles [3].

The other underlying paradigm of ASIA-syndrome is due to the role of adjuvants in immune stimulation. Over decades, adjuvants have been an essential component of experimental studies of the immune system due to their ability to activate various immune cells, thus boosting and speeding up immune response [4]. Also, adjuvants have been widely used beyond immunology laboratories. Taking into account immunostimulatory properties of adjuvants, it is no surprise that a majority of these substances that were considered safe cause autoimmune reactions [5].

Background

Before Professor Yehuda Shoenfeld proposed the term "ASIA-syndrome", the incidence of post-vaccination autoimmune diseases had not been studied properly. Similar conditions were also reported after tattooing, breast implantants surgery, Persian Gulf syndrome (a condition including such symptoms as arthralgia, muscular weakness, joint pain, fatigue, headache, memory disorders, cognitive disorders and higher susceptibility to infections, which were reported by American military men after the Gulf War in 1991) and other pathologies [4]. Cases of optic neuritis and myelitis were observed after tetanus toxoid vaccination [6]. As for flu vaccine, episodes of vasculitis, Reiter disease and Gullian-Barre syndrome were reported [4, 6]. There were cases of immune thrombocytopenic purpura and diabetes mellitus after vaccination against measles, mumps and rubella [6]. Virus hepatitis B vaccine is highly associated with such autoimmune disorders as nodal fever, polyarthritis, immune thrombocytopenia, severe myasthenia, uveitis, Reiter's syndrome, systemic lupus erythematosus, and Evan syndrome. Scientific literature sources describe development of chronic fatigue syndrome in females with silicone breast implants after hepatitis B vaccination. Thus, it can be assumed that the immune response to vaccination could have been enhanced by silicone as an adjuvant [7, 8].

Available information led to the conviction that adjuvants are a predisposing factor for development of post-vaccination autoimmune reactions [9]. This information was updated by Doctor Ye. Shoenfeld. In his papers, the scientist argues that the immune system discriminates Toll-like receptors on WBCs and triggers adjuvant-induced immune response [9].

Several adjuvants, such as virosomes for HBV, HPV and HAV, MF59 in some viral vaccines, against viral and parasitosis and cholera toxin for cholera, have been described. Some adjuvants were mentioned as factors predisposing to autoimmune disorders. For instance, mineral oil adjuvants were believed to be a cause of sclerogenic lipogranulomas [6]. However, the two principal adjuvants causing autoimmune reactions were and are aluminum and silicone [4]. It was found out that aluminum in hepatitis A and hepatitis B vaccines, tetanus toxoid vaccines, flu vaccines and pneumococcus vaccine contribute to the development of multiple sclerosis, chronic fatigue syndrome and polymyalgia rheumatica [10].

Table 1. *The diagnostic criteria for ASIA syndrome*

Major Criteria	Minor Criteria
1. Exposure to external stimuli (infection, vaccine, silicone, adjuvant) before the onset of clinical symptoms 2. The appearance of typical clinical manifestations: а. Myalgia, myositis, or muscle weakness б. Arthralgia and/or arthritis в. Chronic fatigue, un-refreshing sleep, or sleep disturbances г. Neurological manifestations (especially associated with demyelination) д. Cognitive impairment, memory loss е. Fever, dry mouth 3. Typical histological findings after biopsy of offending organs 4. Removal of offending agent results in improvement of symptomatology	1. Appearance of antibodies directed against the adjuvant suspected to be involved 2. Secondary clinical manifestations (irritable bowel syndrome, interstitial cystitis, Raynaud's syndrome, etc.) 3. Evolvement of an autoimmune disease (multiple sclerosis, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis) 4. Antigens specific for human leukocytes (HLA DRB1, HLA DQB1)

Besides, there were reports on Persian Gulf syndrome which developed as a result of Toll-like receptors exposure to WBCs after an injection containing aluminium hydroxide [11]. As for silicone, literature sources describe cases of connective tissue disorders, such as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis after silicone enters the body [6].

There is information on development of autoimmune disorders after injections of filler adjuvants or tattoos. However, it was noted that an autoimmune process after tattooing can be induced by several therapies. For instance, granulomatous reaction to tattooing was observed after intense light pulse procedure for face skin rejuvenation [12]. In some cases, authors were unable to determine the exact cause of granulomatous reaction, which can be triggered by any of numerous various pigments, especially red and black, and excipients injected into skin. Besides, there are reports on sarcoid granuloma which developed after alpha interferon therapy for head melanoma [13].

These studies, among others, were the basis for the study by Doctor Ye. Shoenfeld et al., which was a momentum for the introduction in 2011 of ASIA-syndrome as a nosologic entity and formation of diagnostic criteria (Table 1). Currently, Shoenfeld's syndrome is suspected in the presence of two major criteria or one major and two minor criteria [4].

Etiology and Pathogenesis

ASIA-syndrome is a multi-factor pathology triggered by a complex combination of exogenous and endogenous (genetic) factors. Environmental factors are a key criterion for ASIA-syndrome and are responsible for traditional signs of Shoenfeld's syndrome. After exposure to external environmental triggers, patients more often have symptoms of chronic fatigue and general weakness [14, 15]. The most well-studied triggers — silicone and aluminium — can irritate immune system and induce autoantibody production [16]. Silicone is known to cause autoimmune processes; however, initially it was considered inert and non-immunogenic. Silicone breast disease is a classic example of Shoenfeld's syndrome [17]. Numerous studies demonstrated that silicone can trigger an autoimmune inflammatory process in two possible ways: by boosting immune response and by molecular mimicry [18]. Once in the body, silicone causes an acute inflammatory process and enhances cytokine production [19]. A connective tissue capsule is formed in the area of silicone implantation, which is infiltrated with CD4+ lymphocytes, macrophages and multinucleated giant cells, surrounds the implant and forms a so-called siliconoma [20]. Also, the body can experience a cross-reaction between silicone and natural structures in human connective tissue, such as glycosaminoglycans [21].

Genetic factors are considered secondary diagnostic criteria effecting predisposition to Shoenfeld's syndrome [22]. Genetic association is mediated by HLA antigens involved in autoimmune disorders. Human leukocytal antigen system is a genomic locus of the major histocompatibility complex, the most polymorphous gene cluster of mammal genome [23]. The presence of HLA-DRB1, HLA-B27 and PTPN22 is the most common genetic background of ASIA-syndrome [15].

Epidemiology

The information on the epidemiology of the disease is scarce. Over a period from 2011 to 2016, there were more than 4000 documented ASIA-syndrome cases with various clinical severity and a various history of adjuvant exposure, a majority of which were associated with silicone implants and the use of cosmetic fillers containing mineral oils; by 2021, the number of cases doubled [24]. The mean age on onset was 37 years old, the majority of patients were women (89 %), and the average period between adjuvant stimuli and autoimmune conditions development was 16.8 months (range: 3 days to 5 years) [24].

ASIA-Syndrome in Connective Tissue Disorders:

Undifferentiated connective tissue disease

Undifferentiated connective tissue disease is an autoimmune disease and has non-specific signs and symptoms, the manifestation of which is associated with exposure to adjuvants. Undifferentiated connective tissue disease is the most common in patients who were vaccinated against hepatitis B virus [22, 25]. Studies of the effects of various adjuvants on patients with undifferentiated connective tissue disease vs. controls demonstrated that patients who had been exposed to adjuvants (vaccines or silicone) suffered from autoimmune complications or had a higher rate of typical symptoms of Shoenfeld's syndrome (general weakness, irritable bowel syndrome and fatigue) [14].

Systemic lupus erythematosus

Systemic lupus erythematosus is characterised by the presence of a wide array of autoantibodies in patients

with multisystemic involvement [26]. The possible pathogenesis mechanism is associated with mitochondrial DNA which is an autoimmune antigen and which can be targeted by autoantibodies [27]. A systemic review of selected studies and case control studies demonstrated that vaccines, specially hepatitis B and HPV vaccines, were associated with a higher risk of systemic lupus erythematosus [28]. Another study describes several various cases of disease after DTwP vaccination. The article demonstrates that aluminum adjuvant can initiate systemic lupus erythematosus by stimulating cell death, thus allowing free movement of nuclear antigens and potential activation of Toll-like receptors. Besides, aluminum-induced production of interleukin-6 can cause a cascade of reactions that eventually trigger autoantibody synthesis facilitating further disease progression [29].

Systemic sclerosis

Systemic sclerosis is a rare connective tissue disease associated with vasculomotor disorders, fibrosis and affected organ atrophy [30]. The main cause of disease is still unknown; however, it is assumed that this pathology is a result of environmental, autoimmune and genetic factors [31]. Certain HLA types were identified in systemic sclerosis [32], including HLA-DRB1, which was associated with ASIA-syndrome [22]. Various agents causing systemic sclerosis, such as CMV, Epstein-Barr virus and B19 parvovirus, as well as non-organic pathogens (quartz powder) or organic solvents, toluene, xylene, trichlorethylene and PVC [33], have been studied.

ASIA-Syndrome in Endocrine Disorders:

Primary adrenal insufficiency

Primary autoimmune adrenal insufficiency, or Addison disease, is a disease where adrenal cortex is unable to efficiently produce glucocorticoids and mineralocorticoids [33]. Clinical manifestations of this disease are fatigue, nausea, dizziness, tendency to consumer larger amounts of salt and skin and mucous hyperpigmentation [34]. Patients with Addison disease have anti-ferment-21-hydroxylase autoantibodies, a ferment participating in synthesis of adrenal hormones [35].

Literature sources describe association between adrenal insufficiency and exposure to adjuvants. A 9-year-old patient had adrenal insufficiency after hepatitis B vaccination [21]. There is a report on a 21-year-old patient who had adrenal crisis one week after flu + DTwP vaccination [36]. Since the patient did not have a history of adrenal insufficiency, but his blood draw showed a higher level of anti-ferment-21-hydroxylase autoantibodies, the patients was diagnosed with autoimmune Addison disease.

Type 1 diabetes mellitus

Type 1 diabetes mellitus is a disease associated with hyperglycemia resulting from immune-mediated destruction of insulin-secreting pancreatic β-cells by autoantibodies to Langerhans islet cells, insulin, glutamic acid decarboxylase and protein tyrosine phosphatase [37, 38].

In their paper, Ruhrman-Shahar N. et al. (2017) reported a case of a 14-year-old girl who had severe polydipsia, polyuria and weakness 3 weeks after DTwP vaccination [28]. The patient had autoantibodies to glutamic acid decarboxylase and islet cells and was diagnosed with type 1 diabetes mellitus. Of note, this case was one of the four other cases of patients who were vaccinated against DTwP and had autoimmune diseases. Also, in 1990s there were high rates of type 1 diabetes mellitus in children who were vaccinated with four doses of Hib vaccine at the age of 3, 4, 6, and 14 months, as compared to children who were vaccinated once at the age of 14 months [1].

ASIA-Syndrome in Neurological Disorders:

Myalgic encephalomyelitis/chronic fatigue syndrome

Fatigue of unknown origin lasting for over 6 months is a primary sign of myalgic encephalomyelitis and is associated with such symptoms as myalgia, arthralgia, impaired memory or attention concentration, headache, disturbing dreams, painfull lymph nodes and weakness after physical activity [39]. Idiopathic chronic fatigue syndrome is similar to post-infection fatigue; however, patients did not have pathogens, thus an idea of various pathogens and toxic compounds appeared [40]. For instance, vaccines which contain several components can induce chronic fatigue syndrome [40]. Currently, aluminum adjuvants in vaccines are believed to cause chronic fatigue syndrome [41].

Guillian-Barre syndrome

Guillian-Barre syndrome is an acute autoimmune neuromuscular disease that causes muscle weakness and palsy which can result in respiratory distress and death [41]. The cause-and-effect relationship between vaccines and Guillian-Barre syndrome was established back in 1970s during H1N1 vaccination in US army men.

According to the report, for every 100,000 vaccinated persons there was 1 case of Guillian-Barre syndrome, and the vaccination program was closed [5].

Multiple sclerosis

Multiple sclerosis is an autoimmune CNS disorder associated with amyelination and progressive palsy [42]. In 1994, France had a mass hepatitis B vaccination campaign as recommended by the World Health Organisation in early 1990s. Following the campaign, there were reports on onset or relapse of multiple sclerosis, and a hypothesis appeared that hepatitis B vaccine triggered cases of multiple sclerosis in vaccinated persons [43]. Recently, there have been discussions of multiple sclerosis progression in persons with risk factors after COVID-19 vaccination, requiring further studies [44].

Other Manifestations of ASIA-Syndrome

In addition to connective tissue, endocrine and neurological disorders, scientific literature describes non-Hodgkin lymphomas, sarcoidosis, orthostatic tachycardia, myositis, pulmonary fibrosis and Crohn's disease. Chronic immune system stimulation, exposure to silicone breast implants, hepatitis B vaccination, flu and DTwP vaccination were associated with the mentioned conditions [21, 45].

Prolonged immune system activation is considered the primary mechanism facilitating inflammatory reaction. Adjuvant-induced chronic stimulation is associated with a high risk of lymphoma. Following silicone implantation, chronic B-cell stimulation can result in pseudolymphoma progressing to well-defined non-Hodgkin lymphoma [45]. Besides, high non-Hodgkin lymphoma morbidity is observed in other autoimmune diseases, especially in Sjorgen's syndrome [46].

Thus, numerous autoimmune reactions associated with ASIA-syndrome develop after adjuvant entering into the body. Although the benefit of vaccines outweighs the risk of side effects, the role of adjuvants in autoimmune disease development should not be underestimated.

Conclusion

The article discusses the causes of development and a wide array of manifestations of ASIA-syndrome; it describes pathologies developing almost in any systems of a human body and demonstrates their correlation with autoimmune processes. Long before the term "Shoenfeld's syndrome" was introduced, clinical presentations of this condition were mentioned in literature; however, an approach for pathology diagnosis was not formulated in detail, and emerging symptoms were described as non-specific. ASIA-syndrome has definitely clarified the role of adjuvants in the development of autoimmune processes. It should be taken into account in the development of safe vaccines, silicone implants and other medical devices with minimal side effects. Also, healthcare professionals should raise patients' awareness of side effects of some cosmetic procedures and silicone implants. It is advisable and well-timed to include aetiology, pathogenesis, diagnosis and management of ASIA-syndrome as a separate nosological entity to academic and reference guides for students, registrars, postgraduates and various medical professionals.

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ВЗАИМОСВЯЗЬ МИКРОРНК С ТРАНСПОЗОНАМИ В РАЗВИТИИ САХАРНОГО ДИАБЕТА 1 ТИПА

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Relationship of MicroRNAs with Transposable Elements in Type 1 Diabetes Development

Резюме

В обзорной статье представлены данные об участии эпигенетических факторов в этиопатогенезе сахарного диабета 1 типа. Это отражается, в первую очередь, в изменениях экспрессии микроРНК, которые влияют на транскрипцию генов, вовлеченных в аутоиммунные реакции, разрушение бета-клеток островков Лангерганса и продукцию инсулина. Однако причина наблюдаемых эпигенетических изменений до сих пор не ясна. В эволюции источниками генов микроРНК являются транспозоны, занимающие до 45 % всей последовательности ДНК человека и являющиеся драйверами эпигенетической регуляции в онтогенезе. Они являются источниками последовательностей транскрипционных факторов и сайтов связывания с ними. Особенности распределения транспозонов в геноме могут стать причиной изменения количества 5'VNTR (variable number of tandem repeats) — повторов промоторной области гена инсулина и инсерций HERV в область генов *HLA*, что отразится на характере их экспрессии. В связи с этим сделано предположение, что причиной развития сахарного диабета 1 типа может служить дисбаланс активации транскрипции транспозонов, что способствует изменению экспрессии специфических микроРНК и белок-кодирующих генов, а также способствует развитию аутоиммунного ответа. Провоцирующими факторами могут быть индивидуальные особенности распределения транспозонов в геноме, вирусные инфекции и стрессовые воздействия. Анализ научной литературы подтверждает предложенные механизмы развития болезни, поскольку доказаны глобальная роль ретроэлементов в гормональной регуляции, чувствительность транспозонов к экзогенным вирусным инфекциям и стрессовым воздействиям, экспрессия эндогенных ретровирусов HERV-W у большинства больных сахарным диабетом 1 типа с активацией аутоиммунного ответа. Анализ базы данных MDTE DB (miRNAs derived from transposable elements database) показал происхождение от транспозонов 12 ассоциированных с сахарным диабетом 1 типа микроРНК (miR-192, miR-224, miR-31, miR-320c, miR-326, miR-340, miR-342, miR-44661, miR-548c, miR-652, miR-95), использование которых может стать основой таргетной терапии.

Ключевые слова: *аутоиммунные реакции, инсулин, микроРНК, ретроэлементы, транспозоны, сахарный диабет 1 типа, эндогенные ретровирусы*

Конфликт интересов

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

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Abstract

The review article describes the involvement of epigenetic factors in type 1 diabetes mellitus (T1DM) etiopathogenesis. The disease is characterized by changes in expression of microRNAs that affect the transcription of genes involved in autoimmune reactions, destruction of beta cells and insulin production. However, the cause of the observed epigenetic changes is still unclear. In evolution, the sources of microRNA genes are transposable elements, which occupy up to 45% of the entire human DNA sequence and are drivers of epigenetic regulation in ontogenesis. They are sources of transcription factor sequences and binding sites for them. Features of the genome distribution of transposable elements can cause changes in

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the number of 5'VNTR (variable number of tandem repeats) — repeats of insulin promoter region and HERV insertions into HLA genes, which affects their expression. Therefore, I assume that the cause of the development of type 1 diabetes mellitus may be an imbalance in transcription activation of transposons, which contributes to changes in the expression of specific microRNAs and protein-coding genes, and also contributes to autoimmune response development. Triggers for this may be individual features of genome distribution of transposons, viral infections and stress. An analysis of the scientific literature confirms my proposed mechanisms for T1DM development, since the global role of retroelements in hormonal regulation, the sensitivity of transposable elements to exogenous viral infections and stress, and HERV-W expression of the majority of patients with T1DM with activation of the autoimmune response have been proven. Analysis of the MDTE DB (miRNAs derived from transposable elements database) database showed the transposon origin of 12 T1DM-associated microRNAs (miR-192, miR-224, miR-31, miR-320c, miR-326, miR-340, miR-342, miR-44661, miR-548c, miR-652, miR-95), the use of which can become the basis for targeted therapy for T1DM.

Key words: *autoimmune reactions, insulin, microRNA, retroelements, transposable elements, type 1 diabetes mellitus, endogenous retroviruses*

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BCP — beta cells of pancreas, DM — type 1 diabetes mellitus, HERV — human endogenous retrovirus, HLA — human leukocyte antigen, *INS* — insuline gene, Treg — regulatory T-cells (CD8+ lymphocytes), UTR — untranslated region, VNTR — variable number of tandem repeats

Introduction

According to the International Diabetes Federation (IDF), diabetes affects 8.8 % of the adult world population. 10–15 % of cases are type 1 diabetes mellitus (DM1) [1], which is characterised by uncontrolled immune response to beta cells of pancreas (BCP) and their depletion [2]. Autoantibody synthesis starts several years before clinical manifestations of DM1 with inflammatory processes in pancreas, infiltration with T-lymphocytes and other immune BCP cells [3]. One method to develop new therapies for DM1 can be the study of genetic factors of this disease, since DM1 heritability is assumed to be 88 %, and monozygotic twins concordance — 70 % [4]. 2 % of DM1 patients are diagnosed with a monogenic disease causes by MODY (Maturity-Onset Diabetes of the Young) gene mutations [5], with the most common mutations being in genes *HNF4A, GCK, HNF1A, HNF1B* [6].

Genetic testing, such as genome-wide association study (GWAS), made it possible to identify association between DM1 and polymorphic variants of a number of various genes: *GSDMB* (encodes gasdermin B), *C1QTNF6* (a protein associated with C1q and tumour necrosis factor), *ZPBP2* (zona pellucida-binding protein 2), *CTSH* (catepsin H), *SIRPG* (signal-regulating protein gamma). Besides, the association of DM1 with allelic variants of the following genes has been identified: *AFF3* (a coding protein, a member of AF4/FMR2), *RPS26* (ribosomal protein S26), *DEXI* (dexamethasone 1), *CFDP1* (craniofacial development protein 1), *ORMDL3* (ORM1-like protein 3), *SMARCE1* (SWI/SNF-bound, matrix-associated actin-dependent chromatin regulator), *UBASH3A* (ubiquitin-associated SH3 domain-containing protein A) [7]. DM1 is also associated with allelic variants of the following genes: *PTPN22* (a protein product — nonreceptor thyrosine phosphataze, type 22), *CTLA-4* (T-lymphocyte-associated cytotoxic protein), *IL2RA* (interleukin 2 receptor alpha-subunit), *PTPN2* (nonreceptor thyrosine phosphataze, type 2), *IFIH1* (interferon-induced helicase), *BACH2* (main leucine zip-per transcription factor), *UBASH3A* (ubiquitin-associated SH3 domain-containing protein A), *GLIS3* (Gli-like protein 3) [8]. However, it is currently not possible to explain the impact of such a number of genes and, moreover, to use obtained data to develop diagnostic panels and new therapies. A study of the role of epigenetic factors in DM1 aetiopathogenesis is far more promising, because changes caused by these factors are reversible; therefore, they can be targeted in order to correct and treat DM1. Epigenetic factors include DNA methylation, histone modification and RNA interference using non-coding RNAs [9].

The most common non-coding RNA is micro-RNA. They are short RNA molecules of 18–25 nucleotides, which regulate gene expression at the posttranscriptional level. The majority of micro-RNA genes is localised in introns, however, they can also be localised in intergenic sequences, untranslated regions (UTR) and exons. They primarily down-regulate mRNA transmission in their target genes due to complementary binding with 3'UTR. Exceptions are miR-10a, which binds with c 5'UTR in ribosomal mRNA and up-regulates its translation; and miR-21, which positively regulates expression of mitochondrial cytochrome (mt-Cytb) [2]. Micro-RNA can affect DM1 development in several ways: causing BCP depletion and functional changes, suppressing insulin

gene expression and stimulating immune response to beta cells (Fig. 1). These effects are implemented by inhibiting or stimulating specific targets with micro-RNA molecules — mRNA genes involved in various signal paths and mechanisms. Paediatric patients with DM1 have increased blood levels of miR-21, which causes BCP apoptosis due to stimulation of caspase-3 production [10]. Similar effects on BCP are observed with miR-375, targeting genes *Aifm1, Gephyrin, Ywhaz, Mtpn*, that participate in insulin exocytosis. Besides, it was noted that miR-375 can down-regulate insulin gene expression [11]. miR-29, the levels of which are increased in serum of DM1 patients [12], stimulates apoptosis by suppressing expression of antiapoptotic proteins [13].

Serum of DM1 patients demonstrates increased levels of miR-26 [12], which targets mRNA of histone methyltransferase gene Ezh2, suppressing regulatory T-cell (Treg) proliferation [14]. Thus, Ezh2 inhibition causes an increase in synthesis of Treg participating in immune response. DM1-associated miR-25 (increased serum expression) down-regulates insulin gene expression (*INS*) [12]. Plasma of DM1 patients demonstrates significantly higher miR-181 expression, which negatively regulates expression of gene *SMAD7,* effecting BCP function [15]. In 2017, Assmann et al. conducted a systemic review and bioinformatic analysis of available scientific information on the role of micro-RNA in DM1 development. As a result, they identified a reliable dysregulation of 11 specific micro-RNAs in DM1 patients as compared to controls: miR-21-5p, miR-24-3p, miR-100-5p, miR-146a-5p, miR-148a-3p, miR-150-5p, miR-181a-5p, miR-210-5p, miR-342-3p, miR-375, miR-1275. miR-21-5p, miR-181a, miR-375 were involved in BCP apoptosis due to inhibition of mRNA of genes *PI3K* and *AKT*with suppression of mTOR pathways; miR-146a-5p — due to inhibition of transcription factor NFκB. miR-24-3p and miR-210-5p targeted cytokines IL6R, LIFR, IL2RB, IFNLR1. Micro-RNAs miR-148a-5p, miR-100-5p, miR-150-5p target mRNA of genes *NFκB, MAPK, PI3K-Akt* in pathways of ubiquitin-mediated protein cleavage [16].

A meta-analysis of data on the association between circulating micro-RNA in serum and plasma of DM1 patients, conducted in 2021, demonstrated a highly reliable increase in expression of 2 micro-RNAs (miR-181, miR-210) and reduction in expression of 1 microRNA (miR-375) vs. healthy controls [17]. Blood mononuclear leukocytes of patients with DM1 had significantly higher expression of miR-326, which promotes autoimmune response due to the impact on mRNA, proteins of which are immune modulators. They include homotype 1 of erythroblastosis tumour virus E26 and vitamin D receptor [18]. Low miR-146 levels in peripheral mononuclear leukocytes are associated with immune response in DM1, evidencing the protective action of this micro-RNA [19]. Autologous-reactive CD8+ T-cells of DM1 patients demonstrate increased expression of miR-510 [20], miR-23b, miR-590 and miR-98, targeting apoptosis regulating genes *Fas, Faslg, Trail, Trail-R2,* effecting increased proliferation of diabetogenic T-cells [21]. Patients with type 1 pre-diabetes demonstrate higher miR-31 expression in CD4+ T-cells, facilitating immune response due to inhibition of transcription factor Foxp3 involved in immune reactions [14].

Based on the above, DM1 development can be impacted by changes in expression of specific micro-RNAs both in pancreatic tissue itself (facilitating BCP apoptosis, impaired insulin synthesis and autoimmune response activation), impacting circulating micro-RNA levels, and in blood cells stimulating their autoimmune response. Therefore, micro-RNAs can be successfully

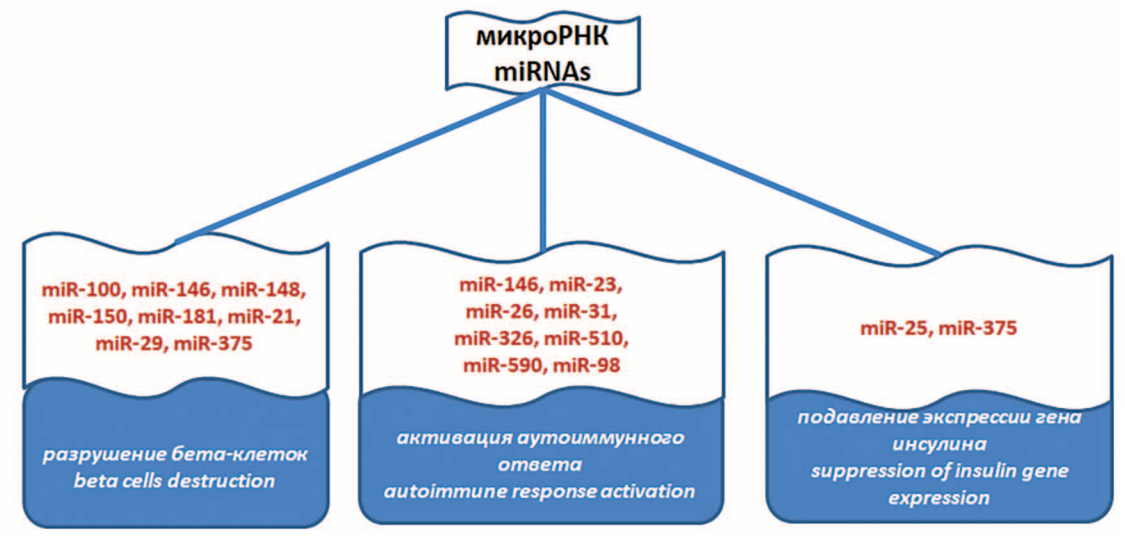

Figure 1. *Scheme of the mechanisms of microRNAs influence on T1DM development*

used as an object for epigenetic therapy impacting both T-cells (inhibiting differentiation of their pathogenic phenotypes) and BCP (facilitating their functional restoration). In particular, low miR-146 levels in mononuclear leukocytes are associated with severe DM1. Administration of miR-146 mimetics in animal models alleviates diabetes and inhibits autoimmune processes [22]. It is possible to use such mimetics and other micro-RNAs, such as miR-191 and miR-342, expression of which is reduced in regulatory T-cells of patients with DM1 [20]. It is also necessary to search for root causes, that cause imbalance in expression of micro-RNAs and other factors activating production of anti-BCP autoantibodies.

Micro-RNAs and transposones in the development of type 1 diabetes mellitus

Transposones have become an unexpected important source of micro-RNA genes during evolution [23]; they are scattered all over human genome and are able to move within genome, including gene introns. Together with their repeats, transposones account for over 2/3 of all human DNA sequences [24]. MDTE DB, a database on the origin of human micro-RNAs from transposones, has been formed [23]. Transposones are classified as retroelements (they form repeats from their own cDNA transcripts, which are integrated into a new gene locus) and DNA-transposones (they move within the genome using "cut and paste" mechanism). Retroelements can have long terminal LTR repeats (including endogenous retroviruses (HERV)) or cannot have them (non-LTR retroelements). Autonomous non-LTR retroelements (encoding own reverse transcriptase and endonuclease, which are essential for transpositions) are LINE1, LINE2, PLE, DIRS. Non-autonomous retroelements using enzymes of other transposones include SINE (also Alu) and SVA (SINE-VNTR-Alu) [25]. A comparative analysis of micro-RNAs presented in MDTE DB with scientific literature allowed identifying 12 micro-RNAs originating from transposones, the expression of which is specifically changed in patients with DM1. Three micro-RNAs (miR-335, miR-340, miR-548c) out of 44 presented in a paper by Takahashi et al. [26] originated from transposones [23]. Two micro-RNAs (miR-342 и miR-652) out of 41 published in a study by Ferraz et al. originated from transposones [27]. Out of 22 micro-RNAs identified by Morales-Sanchez et al., miR-31 and miR-4661 originated from retroelements [28].

For some micro-RNAs, which originate from transposones, the expression of which is changes in DM1 patients (Table 1), the mechanism of impacting the disease has been identified. For example, miR-326 targets mRNA of genes modulating immune system: *VDR* (vitamin D receptor) and *ETS-1* (homotype of erythroblastosis tumour virus E26) [29]. miR-31 targets mRNA

Table 1. *Expression changes of transposable elements-derived miRNAs in patients with T1DM*

МикроРНК/ MiRNA	Характер изменения экспрессии при СД1 (ткань)/ Expression change in T1DM (tissue)	Транспозон — источник возникновения/ Transposable element — source of origin	Автор исследования/ Reference
miR-192	повышение (кровь)/ increase (blood)	LINE2	[35]
miR-224	повышение (моча)/ increase (urine)	ДНК-транспозон MER135 DNA-transposon MER135	[34]
miR-31	понижение (кровь)/ decrease (blood)	LINE2	[28, 30]
miR-320c	повышение (кровь)/ increase (blood)	LINE1	[33]
miR-326	повышение (ткань БКПЖ)/ increase (pancreatic islet tissue)	ДНК-транспозон hAT-Tip100 DNA-transposon hAT-Tip100	[18]
miR-335	повышение (кровь)/ increase (blood)	SINE-MIR	[26]
miR-340	повышение (кровь)/ increase (blood)	ДНК-транспозон TcMar-Mariner DNA-transposon TcMar-Mariner	[26]
miR-342	повышение (кровь)/ increase (blood)	SINE/tRNA-RTE	[27]
miR-4661	понижение (кровь)/ decrease (blood)	LTR-Gypsy	[28]
miR-548c	повышение (кровь)/ increase (blood)	ДНК-транспозонTcMar-Mariner DNA-transposon TcMar-Mariner	[26]
miR-652	повышение (кровь)/ increase (blood)	ДНК-транспозон hAT-Tip100 DNA-transposon hAT-Tip100	[27]
miR-95	повышение (моча)/ increase (urine)	LINE2	[32]

of gene of transcription factor FOXP3, which regulates development and functions of regulatory T-cells [30]. miR-95, which originates from LINE2 [23], also interacts with FOXP3 [31]. Increased miR-95 levels are observed in patients with DM1 and are significantly higher in a high risk of severe diabetic nephropathy progression [32]. miR-320c targets mRNA of genes *STAT4, CCR7, RASGRP1, SH2B3,* the expression products of which are involved in regulation of endocytosis, cell cycle and signal pathway of transforming growth factor TGF-beta. Therefore, increased miR-320c levels in DM1 are associated with damaged BCPs [33]. Urine of DM1 patients demonstrate higher levels of miR-224 targeting mRNA of gene *SMAD4,* involved in TGF-beta pathways and cell proliferation regulation [34]. DM1-associated miR-192 activates TLR7/8 pathways, promoting T-cell proliferation [35].

The data in Table 1 make it possible to suspect a role played by transposones in DM1 development, a potential manifestation of which is modified expression of transposone-originated micro-DNAs connected with them in single gene networks. Moreover, it is likely that transposones are primary drivers of epigenetic processes in DM1, causing global changes in regulatory networks of the genome and resulting in modified expression of complementary micro-RNAs. It is caused by high sensitivity of transposones to stresses [36, 37] and viral infections [38, 39], which initiate pathologic activation of transposones and result in DM1. An important role can be participation of transposones in endocrine system functioning (Fig. 2). Domestication of retroelement MIR-b in the gene of insulin-like growth factor 1 (*IGF-1*) promoted production of a functional domain of its protein product [40]; retroelement ASR (Alu/snaR-related) has been used to form a beta subunit of chorionic gonadotropin [41]. Nuclear receptors of progesterone [42], vitamin D [43] and oestrogens [44] evolved as a result of retroelement exaptation. It is worth mentioning that LINE1 served as a basis for 80 % of sites for binding to transcription factors of all protein-encoding human genes [45]. Besides, transposones were a primary source of transcription factors during evolution [46]. Prolactin gene promoter *Prl* originated from ERV *MER39* [47], arginine-vasopressin 1a gene (*AVPR1A*) — from SVA [48]. ERV was the source of gene enhancers for proopiomelanocortin(*POMC*) [49] and corticoliberin

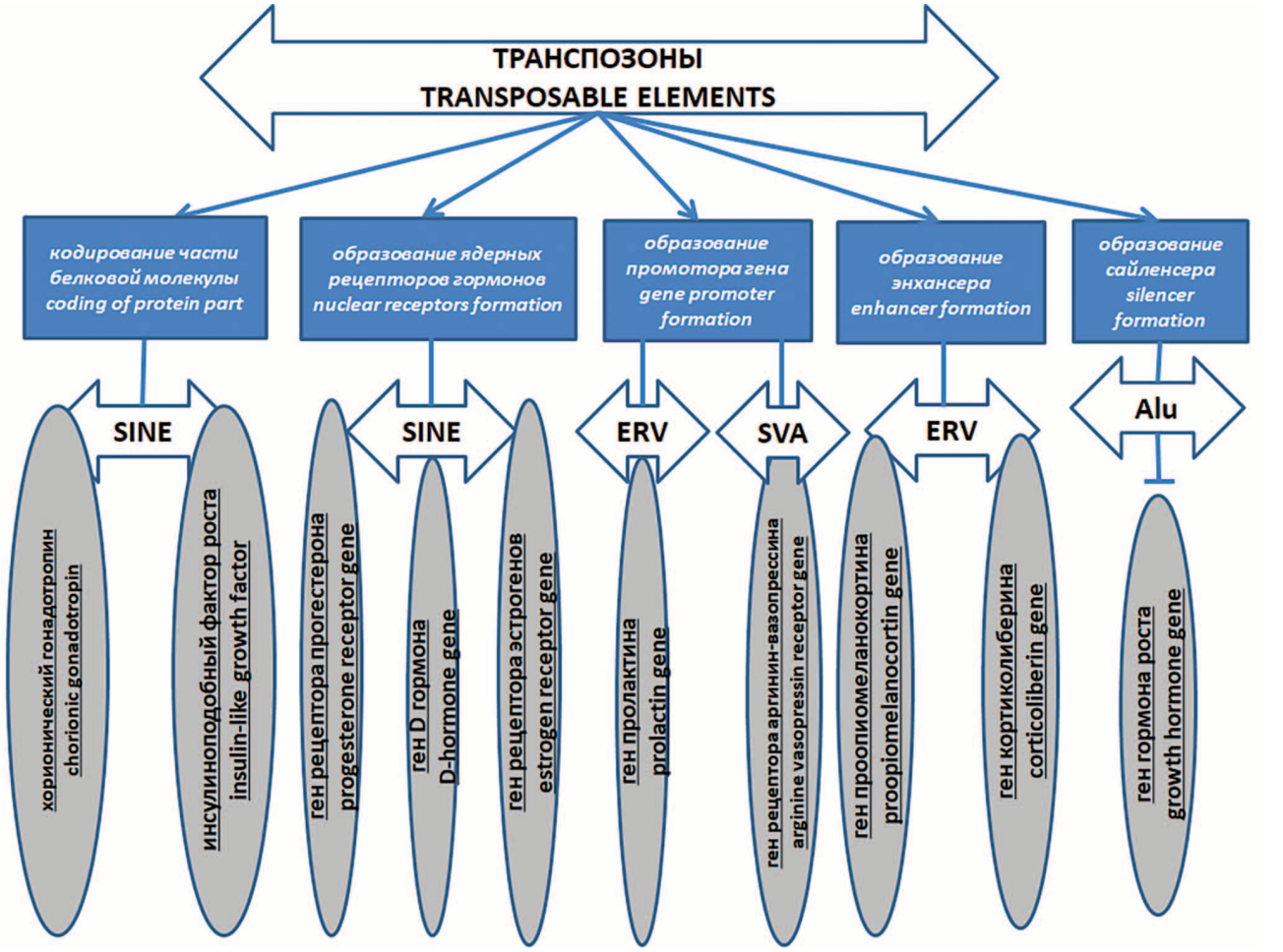

Figure 2. *Role of transposable elements in hormonal regulation*

(*CRH*) [50]. In humans, the gene of growth hormone *GH* is next to 44 *Alu*, a part of which serve as silencers [51]. Description of the role of transposones in DM1 aetiopathogenesis requires more attention.

Role of transposones in the development of type 1 diabetes mellitus

Transposones participate in DM1 aetiopathogenesis via various pathways: serving as autoimmune antigens for stimulation of anti-BCP immune response, inhibiting insulin gene expression or having toxic effect on beta cells. Besides, susceptibility to DM1 depends on the features of SVA distribution in promotor regions of genes HLA and insulin. Results of clinical studies in DM1 patients demonstrate the role of retroelements in maintaining autoimmune processes in this pathology. Since transposones can be activated by exogenous viruses [38, 39], DM1 can be initiated by DM1-associated infections caused by enteroviruses [52, 53] and Epstein-Barr virus [54]. It has been demonstrated that exogenous viruses stimulate HERV-K18 expression and interferon production. In turn, HERV-K18 is a source of superantigen, which stimulates autoimmune T-cells [38].

70 % of DM1 patients have envelope protein HERV-W in their blood, which is not only an autoimmune antigen, but also inhibits insulin expression [55] and has toxic effect on BCP [39]. Protein Env of retroelement HERV-W was found in BCP samples of 75 % of patients with DM1 [56]. Initiation by actively expressing retroelements HERV of autoimmune reactions is evidenced by high titres of antibodies to envelope protein HERV-W-Env in children with DM1 [57]. A study of transcription of genes *pol* of endogenous retroviruses HERV-H, HERV-K, HERV-W in children with newly diagnosed DM1 showed a significantly higher level of expression of genes *HERV-H-pol* and *HERV-W-pol* as compared to healthy controls [3]. In mice experiments with DM1, autoimmune reaction induction by retroelements has also been confirmed: proteins Env and GagERV have been found in BCP microvesicules. DM1 progression was accompanied by an increase in anti-Env antibodies and T-cell stimulation under the influence of antigene Gag [58]. Further experiments demonstrated that Gag antigen is also found in stromal cells of pancreatic islets. DM1-resistant mice have Gag transcription in BCP without formation of a protein product, whereas in DM1 mice, mRNA of gene *GAG* is translated on ribosomes with formation of a protein which is specific to activation of autologous-reactive T-cells [59].

DM1 development depends not only on intragenic mutations in *INS* [6], but also on changes in the variable number of tandem repeats (VNTR) in its promotor region [8]. VNTR is an essential component of retroelements SVA, which, like other transposones, can change the number of tandem repeats [9]. SVA have a lot of GC-repeats, therefore, they can form alternative DNA structures, such as G-quadruplexes (G4), which impact transcription. Over 40 % of human genes contain G4-sequences in their promotor region [48]. Formation of tandem repeats using retroelements is a universal property of all living organisms, it being associated with illegitimate recombination and further amplification by gene conversion [60].

VNTR are located 596 bps upstream of the initiation site of *INS* translation. They are divided into long class III pools (141–209 repeats) and short class I pools (26–63 repeats). The latter are associated with DM1 [8]. It is an evidence of possible impact of retroelement activity on disease progression, since non-autonomous SVA, forming VNTR in the promotor area, have sequences, which are identical to autonomous retroelements LINE, which enzymes they use to translocate in the genome. Allele A of single nucleotide polymorphism — 23HphI (rs689) is in linkage disequilibrium with class I VNTR, whereas allele T — with class III VNTR. Also, allele C-2221MspI is in linkage disequilibrium with class I and subclass IIIB, while allele T — with subclass IIIA. Class III VNTR facilitate enhanced insulin expression in thymus gland with later negative selection of autologous-reactive T-cells to insulin (resulting in immune tolerance to insulin and low risk of autoimmune response to beta cells of pancreas) [61]. Also, blood tests in DM1 patients demonstrated the impact of VNTR length in the promotor region of gene *INS* on formation of proinsulin-specific T-cells participating in autoimmune response [62].

As pointed out above, association of allele variants of gene pools with DM1, observed in various studies, cannot be interpreted in terms of disease aetiopathogenesis. The most understandable is DM1 association with allele variants of genes in the major histocompatibility system *HLA,* since the disease is associated with autoimmune damage to BCPs [3]. Approximately 50 % of family cases of DM1 are associated with HLA region on chromosome 6p21 [8]. It correlates with the role of retroelement activation as an object for autoantibody production [3], because HERV serve as regulatory elements of class I genes of the major histocompatibility system HLA-G [50]. Retroelements can impact immune reactions, facilitating DM1 development, by direct insertions in genes of the major histocompatibility system. Changes in the region of C4 complement gene location impact HLA-DQ-mediated DM1 development. At the same time, a study of 220 families with DM1 demonstrated that 77.7 % of genes *HLA-DQ8* and 52.9 % of genes *HLA-DQ2* have HERV-K (C4) insertions [63], which impact regulation of these genes. Indeed, since genes *HLA-DQ*

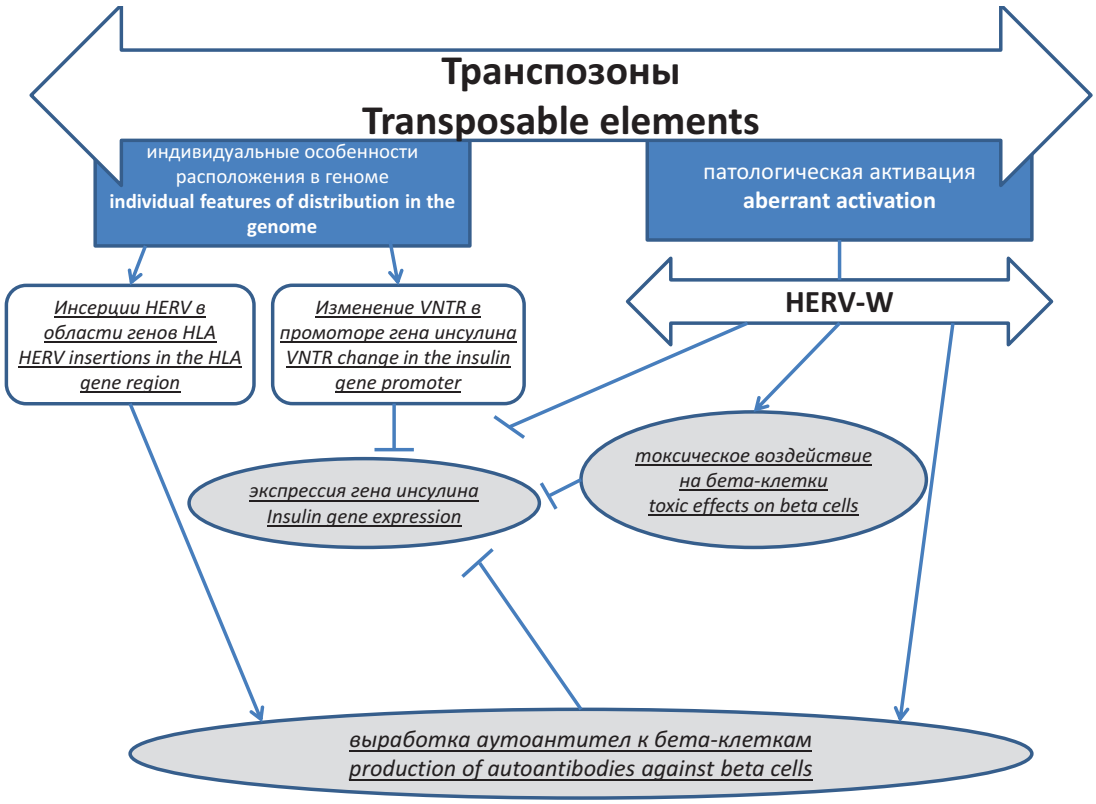

Figure 3. *Scheme of transposable elements effect on the type 1 diabetes mellitus development*

are a factor of DM1 development, the impact of various LTR in this region on disease pathogenesis has been studied. Segregation of LTR located 1,300 bps upstream of *HLA-DQB1* (LTR13) with various HLA-DQ haplotypes was analysed in 284 DM1 patients. It was found out that alleles DQ8/LTR13+ are associated with a risk of DM1 as compared to allele DQ8/LTR13- carriers [64]. In another study of 246 DM1 patients, the association between DQ-LTR3 and disease development was identified. DQ-LTR3 is 90 % homological to HERV-K, evidencing the impact of endogenous retroviruses on the distribution of this sequence [65]. Therefore, pathological transposone activation due to their specific individual location in the genome (affecting VNTR in promotor regions of genes *INS* and HLA group), stresses [36, 37] and exogenous viruses [38, 39] contribute to DM1 development (Fig. 3).

Conclusion

Analysis of scientific literature demonstrated a significant role of heredity in DM1 development. However, studies showed the association between the disease and polymorphic variants or genes, the impact of which cannot be explained. Analysis of data on the impact of epigenetic factors on the disease is of particular interest, because they can be corrected. The change in expression of specific micro-RNAs observed in serum and plasma (circulating micro-RNA), mononuclear leukocytes, T-cells and BCP has been demonstrated. These micro-RNAs impact DM1 development by inducing autoimmune reactions, depleting BCPs and inhibiting insulin production. Experiments demonstrated efficiency of the use of micro-RNA mimetics for DM1 progression suppression, and it can serve as a basis for clinical trials. The root cause of changes in the expression of specific micro-RNAs involved in DM1 pathogenesis is probably pathologic transposone activation. It has been proven that, under the influence of stress factors and exogenous viral infections, individual susceptibility (due to transposone composition and distribution in the genome) facilitates enhanced expression of retroelements. The latter are autoimmune antigens (mainly HERV-W) for production of anti-BCP autoantibodies. Endogenous retroviruses have direct toxic effect on BCPs. Upon activation, transposones show mutual regulation. Retroelements SVA are sources of VNTR in promotor regions of insulin gene, and HERV insertions impact HERV expression. During evolution, sources of genomes of a number of micro-RNAs were transposones. Analysis of literature sources resulted in identification of 12 micro-RNAs originating from them and involved in DM1 development. One can assume that the use of these micro-RNAs as a targeting tool will make it possible to normalise expression of transposones as part of complex therapy of patients with DM1.

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СТЕПЕНИ ТЯЖЕСТИ ПОСТКОВИДНОГО СИНДРОМА: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Severity of Postcovid Syndrome: A Systematic Review

Резюме

Постковидный синдром включает в себя множество состояний и симптомов, как возникших непосредственно в острый период инфекции, так и возникших после его окончания. Целью систематического обзора является определение критериев степеней тяжести постковидного синдрома. Материалы и методы. Для поиска литературных источников использовались следующие ключевые слова: «постковидный синдром», «тяжесть постковидного синдрома», «выраженность постковидного синдрома», «симптомы постковидного синдрома» на русском и английском языках. Для поиска использовались поисковые системы «eLIBRARY.RU — НАУЧНАЯ ЭЛЕКТРОННАЯ БИБЛИОТЕКА» и PubMed.gov. Были включены статьи, в которых представлено исследование пациентов, после подтвержденной лабораторно перенесенной коронавирусной инфекции с остаточными клиническими признаками и/или биохимическими изменениями, проведенное не менее чем через месяц после выздоровления от COVID-19. В анализ включались только публикации последних 3х лет (2020-2023 гг.). Результаты. Всего по двум поисковым системам было найдено 2913 публикаций, после удаления дубликатов, обзоров литературы, клинических исследований лекарственных препаратов, исследований, проведенных на животных, исследований неудовлетворяющих времени проведения после перенесённого COVID-19 и выполненных на лицах, не достигших 18-летнего возраста, для анализа было отобрано 69 статей, удовлетворяющих критериям включения в анализ. Заключение. Анализ литературы последних 3-х лет позволил определить, что наличие и степень тяжести постковидного синдрома, вероятно, может определяться наличием у пациента хотя бы одного признака из представленных в обзоре, развившегося во время или после лабораторно верифицированной инфекции COVID-19 и сохраняющегося в сроки более 4х недель от начала заболевания при условии, что он не может быть объяснен другими причинами.

Ключевые слова: *постковидный синдром, степень тяжести постковидного синдрома, симптомы постковидного синдрома, систематический обзор*

Конфликт интересов

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

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Abstract

Postcovid syndrome includes many conditions and symptoms, both those that arose directly during the acute period of infection and the appearance of new ones. The purpose of the systematic review is to determine the criteria for the severity of postcovid syndrome. Materials and methods. The following keywords were used to search for literary sources: "postcovid syndrome", "severity of postcovid syndrome", "severity of postcovid syndrome" and "symptoms of postcovid syndrome" in Russian and English. We used the search engines "eLibrary.RU — Scientific Electronic Library" and PubMed.gov. Articles were included that presented a study of patients with laboratory-confirmed coronavirus infection at least a month after recovery from COVID-19 with residual clinical signs and/or biochemical changes. The analysis included only publications from the last 3 years (2020–2023). Results. A total of 2,913 publications were found by two search engines. After removing duplicates, literature reviews, clinical studies of medicines, studies conducted on animals, studies unsatisfactory for time after acute COVID-19, and studies performed on persons under the age of 18, 69 articles were selected for analysis that meet the criteria for inclusion in the analysis. Conclusion. An analysis of the literature of the last 3 years has allowed us to determine that the presence and severity of postcovid syndrome can probably be determined by the presence in a patient of at least one of the signs presented in the review that developed during or after a laboratory-verified COVID-19 infection and persisted for more than 4 weeks from the onset of the disease and that cannot be explained by other reasons.

Key words: *postcovid syndrome, severity of postcovid syndrome, symptoms of postcovid syndrome, systematic review*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, ALT — alanine aminotransferase, AST — aspartate aminotransferase, BA — bronchial asthma, GIT — gastrointestinal tract, CHD — coronary heart disease, MI — myocardial infarction, CT — chest computer tomography, NCVI — novel coronavirus infection, PCS — post-COVID syndrome, PTSD — post-traumatic stress disorder, DM— diabetes mellitus, POTS — postural orthostatic tachycardia syndrome, AF — atrial fibrillation, CKD — chronic kidney disease, CCF — chronic cardiac failure, COVID-19 — novel coronavirus infection, CFQ-11 — The Chalder fatigue scale, EQ-5D — European Quality of Life Questionnaire, HADS — Hospital Anxiety and Depression Scale, mMRC — Modified Medical Research Council, SARS-CoV-2 — severe acute respiratory syndrome coronavirus-2, SF-36 — Health Status Survey

Introduction

Post-COVID-19 condition has been widely studied by academic and medical communities.

Currently, there is no globally recognised definition of post-COVID syndrome (PCS). However, in December 2020, the National Institute for Health and Care Excellence (NICE) release a quick COVID-19 guide in cooperation with the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP), which sets forth clinical definitions of this condition at various stages. According to the document, acute COVID-19 symptoms (ACS) last for up to 4 weeks from disease manifestation; ongoing symptomatic COVID-19 persists for 4–12 weeks from the onset; post-COVID-19 syndrome is signs and symptoms evolving during and after COVID-19 infection, lasting for over 12 weeks and not attributed to any other diagnosis [1].

According to the French National Board of Health, long-term persistent COVID-19 means one or several initial symptoms persisting for at least 4 weeks after infection onset, where none of the symptoms can be attributable to another cause [2].

In October 2021, the WHO developed a definition of the clinical condition after COVID-19 using the Delphi methodology: the post-COVID-19 condition develops in subjects with a history of possible or confirmed SARS-CoV-2, usually 3 months after the onset, with symptoms lasting at least for 2 months and not attributable to any other diagnosis [3]. Due to the incidence and clinical significance, this syndrome is officially a disease and was included into the new edition of the International Classification of Diseases, 10th Edition, as "post-COVID-19 condition, unspecified", code U09.9; it is also called post-COVID condition or PCS [4].

It is well-known that the term "long COVID" was introduced by patients in social media to describe persistent post-NCVI symptoms; later, the term has become common in mass media and medical community. In scientific literature it is often used as a synonym to PCS or NICE variant 2 and variant 3 of COVID-19, whereas other scientists differentiate between these conditions,

believing that PCS is a complication of the infection that was cured and the latter is a chronic persistent virus in the body. According to the guidelines developed by the Russian Scientific Medical Society of General Practitioners, National Scientific Society of Infectious Disease Specialists and the Rehabilitation Society (2022), long COVID means clinical manifestations of the disease lasting for 4 to 12 weeks from infection onset; whereas chronic COVID and PCS should be used where symptoms persist for over 12 weeks after disease development [5].

Completed studies show that the recorded incidence of long COVID vary between countries and within a country: United Kingdom 1.6–71 %, Germany 35–77 %, China 49–76 %, Africa 68 %, India 22 %, Bangladesh 16–46 %, Denmark 1 %, Italy 5–51 %, USA 16–53 %, Norway 61 % [6].

According to the ACTIV register (analysis of comorbidities in patients surviving SARS-CoV-2 infection), examination of 9,364 patients demonstrated that more than a half of COVID-19 survivors had disturbing symptoms for a long time (up to 1 year); such symptoms are new or are a result of exacerbation of existing symptoms. Feeling unwell made two thirds of patients seeking unscheduled medical advice during 12 months after discharge from the outpatient unit [7].

A prospective cohort study in children and adults with conformed COVID-19 in Moscow revealed the incidence of post-COVID-19 condition after a 6 and 12-month follow-up of previously hospitalised adults and children. This study demonstrated that a half of adults and one in five children had post-COVID-19 condition [8].

The multicenter clinical epidemiological observational program CORTEX revealed that daily up to 5 patients visited healthcare professionals due to complaints associated with past COVID-19 (up to 30 % of the number of outpatient neurological patients) [9].

PCS manifestations are versatile and vary from neurological symptoms to respiratory, cardiovascular and metabolic conditions and GIT manifestations. Symptoms can develop after recovery or persist after initial disease, and can change or reduce over time.

It is known that SARS-CoV-1 and MERS-CoV, which are two previous outbreaks of a viral infection similar to the current COVID-19 pandemic, had long-lasting symptoms after complete recovery from the primary disease. In their meta-analysis, H. Ahmed et al. found out that approximately one third of patients suffered from long-term anxiety, depression and post-traumatic stress disorder (PTSD) for 6 months after infection manifestation. Besides, they found out that 11–45 % of patients had reduced diffusing lung capacity during a one-year follow-up [10].

Currently, there are no PCS classifications to be used by clinicians, therefore, this topic is a matter of academic interest. However, German scientists developed Post-COVID-19 Functional Status scale (PCFS) to identify the degree of functional dependence and disease severity. This scale involves five stages of functional limitations: 0 (no functional limitations), 1 (negligible), 2 (minor), 3 (moderate) and 4 (significant) [11].

The current situation, where the number of patients with clinical signs of a long-term infection grows and healthcare professionals have to face these manifestations, necessitates the development of criteria for PCS severity in order to provide medical professionals with guidelines for the management of such patients. As more scientific data become available, this approach will probably have comprehensive evidences.

Study Objective

The objective of the systematic review is to identify criteria of PCS severity.

Materials and Methods

The following keywords were used for a search in literature sources: “post-COVID syndrome”, “post-COVID syndrome severity”, “post-COVID”, “long COVID”, “Post-COVID-19 Syndrome”, “post-acute COVID-19 syndrome”. For search in Russian literature, eLIBRARY.RU (SCIENTIFIC ONLINE LIBRARY) was used, whereas PubMed.gov was used for search in English literature sources. The review included the articles describing studies in patients over 18 years of age after a laboratory confirmed NCVI with residual clinical signs and/or biochemical changes, at least one month after recovery from COVID-19. The analysis covered papers which had been published during the previous 3 years (2020–2023) and did not include literature reviews, clinical trials and animal studies. All in all, 2,920 publications were found in both search systems; once duplicate papers, literature reviews, clinical trials and animal studies had been removed, 1,617 publications were included in the analysis.

In the Russian search system, 964 sources were found. 840 articles were excluded because subjects had been examined less than a month after recovery; 116 articles were removed because the mean age of subjects was less than 18 years. Thus, the final analysis included 8 articles in Russian.

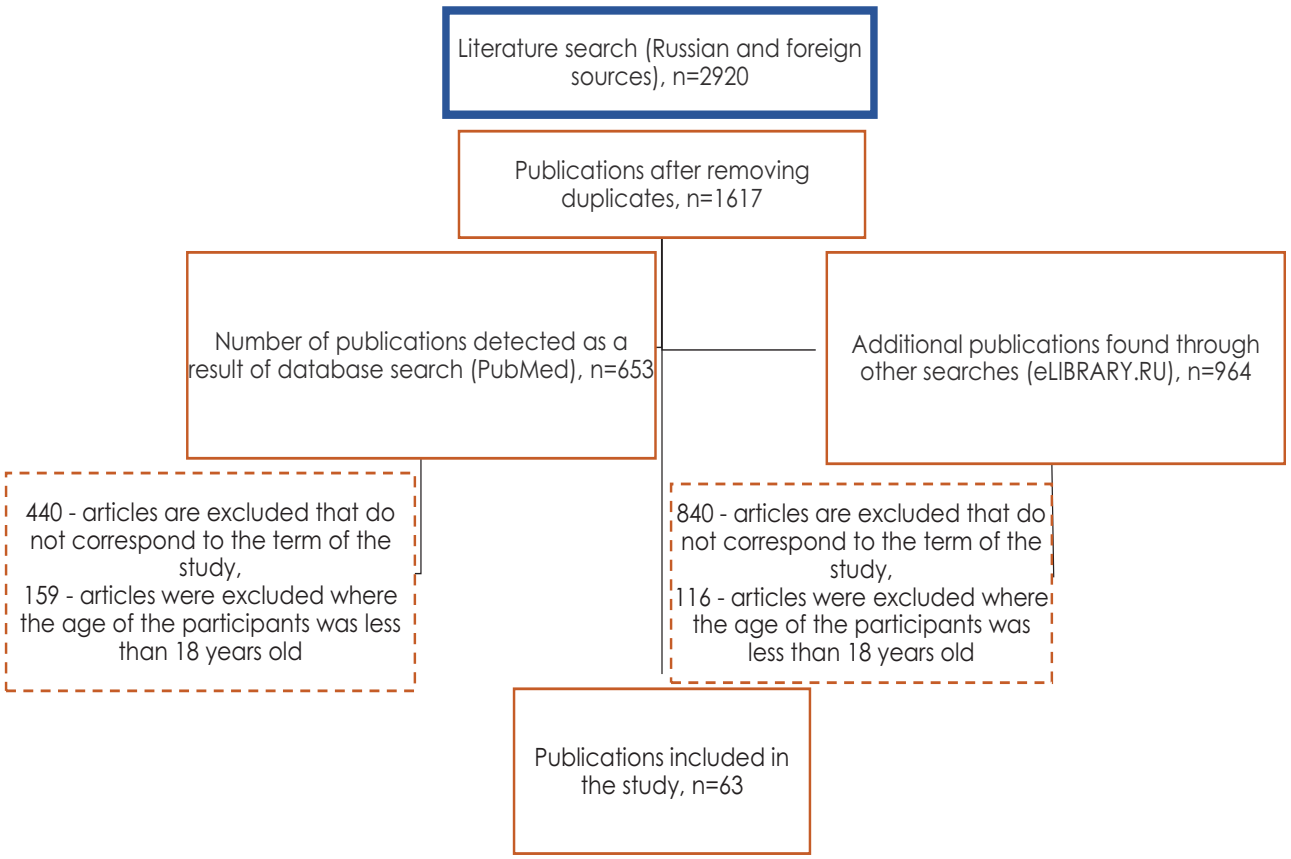

Figure 1. *Research Flowchart*

In the English search system, 653 sources were found. 440 articles were excluded because subjects had been examined less than a month after recovery; 159 articles were removed because the mean age of subjects was less than 18 years. Thus, the final analysis included 54 articles in English.

All in all, 63 articles from the Russian and global systems were selected, which met the inclusion criteria (Fig. 1).

Results

PCS comprises a number of conditions and symptoms, developing both during the acute phase of the infection and after its resolution.

Dominic L. Sykes et al. determined that 86 % of post-COVID-19 patients reported at least one symptom during follow-up [12].

A Swedish study demonstrated that out of 431 COVID-19 patients, 40 % needed another visit to a healthcare provider (GP, emergency room, hospitalisation) 6–8 month after infection onset. In 18 % of cases, a new diagnosis was made. The most common post-COVID-19 conditions were respiratory diseases (56 %), neurological and cognitive disorders (30 %), cardiovascular (11 %) and skin (11 %) diseases [13].

A Dutch retrospective study demonstrated that out of 1,886 subjects in various ethnic groups, 483 patients (26 %, 95 % CI 24–28 %) had lasting symptoms 12 weeks after discharge from the hospital after COVID-19. The most common symptoms reported 3 months after discharge were shortness of breath and fatigue (16 %). It is worth noting that during a one-year follow-up, 40 (14 %) patients still had lasting COVID-19 symptoms [14].

Results of a 6-month follow-up from the global ACTIV register showed that 5.6 % and 6.4 % patients were diagnosed with new diseases during 3 and 6 months post-hospitalisation, respectively. As for the patients with newly diagnosed diseases during 3 and 4–6 months of follow-up, patients with arterial hypertension (AH) were prevailing; they accounted for 41.5 % and 46.7 % in the structure of newly diagnosed diseases. Of note, as compared to the first 3 months, a share of patients with AH increased over 4–6 months of follow-up. Also, the number of patients with newly diagnosed coronary

heart disease (CHD) grew over 4–6 months (22.1 %) as compared to 3 months (9.7 %). Cases of myocardial infarction (MI) were more numerous over 4–6 months as compared to the first 3 months (3.9 % vs 0.8 %). Similar changes were observed for arthritis: growth of 5.2 % over 4–6 months as compared to 4.9 % over the first 3 months; and for newly diagnosed chronic cardiac failure (CCF): growth of 0.8 % of newly registered cases during the first 3 months and 1.3 % of cases over 4–6 months. The remarkable fact is that a share of such newly diagnosed diseases as type 2 diabetes mellitus (DM), atrial fibrillation (AF), stroke, bronchial asthma (BA), cancer, chronic kidney disease (CKD) and DM1 in the total number of newly diagnosed diseases dropped during 4–6 months as compared to the first 3 months [7].

In their meta-analysis, Qing Han et al. found out that fatigue/weakness (28 %, 95 %), shortness of breath (18 %), myodynia (26 %), depression (23 %), anxiety (22 %), memory loss (19 %), impaired concentration (18 %) and insomnia (12 %) were the most common symptoms during a 1-year follow-up [15].

For better understanding the symptoms and conditions, PCS should be divided into groups.

1. Cardiovascular manifestations

In foreign sources, cardiac manifestations of COVID-19 are described with the term "acute COVID-19 cardiovascular syndrome", comprising a wide array of pathologies.

A large US study which included 690,892 COVID-19 survivors and 690,892 controls without NCVI demonstrated that COVID-19 survivors had a higher risk of cardiovascular complications, such as stroke (OR 1.618, 95 % CI 1.545–1.694), AF (OR 2.407, 95 % CI 2.296–2.523), myocarditis (OR 4.406 95 % CI 2.890–6.716), ischemic cardiomyopathy (OR 2.811, 95 % CI 2.477–3.190), cardiac failure (OR 2.296, 95 % CI 2.200–2.396), pulmonary artery thromboembolia (OR 2.648, 95 % CI 2.443–2.870) [16].

A meta-analysis of over 2 million people showed that COVID-19 survivors had an additional 90 % risk of heart failure during 9 months after an acute infection [17].

In a study by Pogosova N. V. et al. under the "COVID-19: a remote follow-up" program, newly diagnosed AH and CHD were recorded in 4.2 % and 1.9 % of patients, respectively [18]. A study of 153 patients a month after COVID-19 showed that both systolic and diastolic blood pressure was higher during the post-COVID-19 period than upon admission in the acute period [19]. In their study, Ayoubkhani D. et al. present data on newly diagnosed cardiovascular complications (MI, stroke, death due to cardiovascular diseases) in 4.8 % of cases after discharge from the hospital after COVID-19 [20].

Maestre-Muñiz M evaluated PCS in persons who were hospitalised with COVID-19, one year after recovery. It was found out that 56.9 % of patients still had PCS a year after an acute infection, while 2 % had newly diagnosed AH and CCF de novo [21].

In 2020–2022, a clinical prospective observational study was conducted to identify the incidence and demonstrate the features of development of newly diagnosed CCF in post-NCVI patients with shortness of breath. The study gradually enrolled 368 patients with shortness of breath, who came to the outpatient clinic; mean time after COVID-19 recovery was 3.5 [1.5; 22.4] months. It was found out that the CCF incidence among post-COVID-19 patients with shortness of breath was statistically higher than in patients without a history of this pathology and made 19.0 % vs 9.8 % ($p = 0.021$). One out of five patients with shortness of breath had a more severe CCF 3.5 months after COVID-19, both as confirmed by clinical tests and blood NT-proBNP levels [22].

It is interesting to note that postural orthostatic tachycardia syndrome (POTS) in post-COVID-19 patients is a separate OCS type which is characterised by sinus tachycardia, postural tachycardia and inadequate sinus tachycardia [23]. Swedish scientists described a series of case studies in 3 patients with POTS 3 months after initial COVID-19 infection [24]. This syndrome is more common in women and is an autoimmune reaction to SARS-CoV-2 infection [25]. Miglis MG et al. described a case study of POTS in a 26-year-old nurse after infection with SARS-CoV-2. Symptoms of vegetative disorders persisted and aggravated for several months after recovery from COVID-19 [26].

A. S. Bagdasaryan et al. found out that, 12 weeks and more after COVID-19, post-COVID tachycardia was diagnosed in 100 % of cases, manifesting as POTS in 64.6 % and as inadequate sinus tachycardia in 19.1 % [27].

A study of 104 patients at the scientific and practical centre for PCS management at the University Clinic of the Federal State Educational Institution of Higher Education Tver Medical State University during a period from September 2021 to August 2022 revealed that, in a majority of patients with PCS, a standard tilt test gives an inadequate response, which is usually an increase in the heart rate by more than 30 bpm and raised systolic blood pressure by more than 20 mm Hg when the patient gets up from the bed [28].

The objective of the study in German COVID-19 survivors was to determine serological markers of cardiac damage (high-sensitivity troponin T and NT-proBNP tests) and to perform highly standardised cardiac imaging using magnetic resonance imaging. Median period between positive COVID-19 test and patient examination was 71 (64–92) days. It was found out that the highly sensitive troponin T values of over 3 pg/mL were recorded in 71 patients (71 %) and were significantly higher (over 13.9 pg/mL) in 5 patients (5 %). If compared to healthy controls, COVID-19 survivors had lower left and right ventricle ejection fraction, higher left ventricle volume and raised native T1 and T2 values as demonstrated by magnetic resonance tomography results [29].

2. Respiratory symptoms

Available data show that lungs are an organ which is most susceptible to COVID-19-induced pathophysiological changes, including diffuse destruction of alveolar epithelium, hyaline membrane formation, vascular damage and, thus, bleeding, fibrous proliferation and lung consolidation [5].

According to a retrospective cohort study conducted in England from January 1 to September 30, 2020, which analysed 47,780 patients, it was found out that respiratory disorders were diagnosed in 14,140 persons (29.6 %) after discharge, and 6,085 of them were newly diagnosed conditions [20].

A Chinese study to evaluate long-term symptoms in COVID-19 survivors 6 months after discharge demonstrated that a majority (22–56 % using various severity scores) of subjects had reduced diffusing lung capacity, as determined by spirography. The analysis included 1,733 patients, and during examination (with the mean follow-up period of 186 days) over a half of them still had abnormal chest computer tomography (CT) results, which independently correlated with lung involvement during the acute phase [30].

Similar data were presented in a study by You J et al., where a month after discharge 83.3 % of patients had abnormal chest CT results with a high share of pulmonary fibrosis. Pulmonary function assessment (spirometry) demonstrated prevailing restrictive disorders (reduced total lung capacity to < 80 % of the normal value or forced vital capacity to < 80 % of the normal value, with normal or increased ratio of forced vital capacity to 1 second forced expiratory volume and reduced diffusing lung capacity to < 80 % of the normal value) [31].

During a 6-month follow-up after recovery from COVID-19, Caruso D et al. found out that 72 % of patients had fibrous changes on CT [32].

Puja Mehta et al. proposed to use the term "post-COVID interstitial lung pathologies (ILD)" for patients with respiratory symptoms (cough, shortness of breath) lasting for over 3 months after acute COVID-19, whereas pulmonary tissue induration should be > 10 % of the lung area [33]. In a majority of cases, post-COVID pulmonary fibrosis does not progress; however, persistent interstitial changes in lungs are often associated with chronic respiratory failure and hypoxaemia, induced by physical load; thus, they impair quality of life and prognosis for patients and require adequate treatment.

In a French prospective cohort study, patients were examined 4 months after hospitalisation with COVID-19. During a phone call, 244 patients reported at least one symptom that they had not had before COVID-19, and newly diagnosed shortness of breath was recorded in 16 %. Chest CT was performed in 171 patient and demonstrated fibrous damage and ground-glass in 19.3 % and 42.4 % of patients, respectively [34].

Also, during the first study in the United Kingdom which reported long-lasting symptoms in COVID-19 survivors, it was found out that newly diagnosed shortness of breath was reported in 65.6 % of cases in ICU patients and in 42.6 % in therapeutic patients [35].

In a single-site prospective cohort study, 183 patients reported persistent symptoms 35 days after recovery from COVID-19, including 58 patients with shortness of breath and 46 patients with cough [36].

Lindahl A. et al. found out that 90 % of patients had several symptoms six months after inpatient treatment of COVID-19. According to available information, shortness of breath and cough were recorded in 66 patients (70 %) and 57 patients (61 %), respectively. Shortness of breath was assessed using mMRC score; the majority of men reported grade 1, while the majority of women — grade 2 [37].

According to the global ACTIV register, 9,364 patients were interviewed 3 months after recovery from COVID-19, and it has been shown that 38.7 % of respondents complained of shortness of breath [7].

An examination of 65 students from Tver State Medical University aged 18 to 25 years in post-COVID period demonstrated that the incidence of cough and shortness of breath was 7.7 % [38].

Xiong Q et al. showed that after a mean period of 79 ± 17 days (a period between first signs of COVID-19 and completion of questionnaire about persistent long-term symptoms after recovery), respondents reported a symptom — sore throat [39]. During the follow-up after 6 months after discharge from hospital after COVID-19, this symptom was recorded in 4 % of cases (69 patients out of 1,655 examined subjects) [30].

3. GIT manifestations

Literature sources mainly present information on aggravation of chronic gastrointestinal (GIT) diseases, such as gastroesophageal reflux disease, stomach ulcer, irritable bowel syndrome [40-42]. The main manifestations of GIT disorders are diarrhea and abdominal pain, which can persist for up to 4 weeks after the acute period of COVID-19 and are non-specific [43]. A number of Russian and foreign studies demonstrated that the incidence of bowels motor function disorders (diarrhea, constipation) varied from 3.6 % to 48 %, abdominal pain of any location — from 9 % to 32 % [44-46].

Hepatobiliary involvement is also temporary and is characterised by the development of acute hepatitis, drug-induced liver injury and aggravation of chronic hepatobiliary disorders [47]. Increased ALT, AST and bilirubin levels are temporary and are directly associated with the severity and therapy of COVID-19 [48]. Persistent liver changes are observed in pre-existing diseases [49]. Thus, these studies mainly present GIT changes during the acute phase of continuing COVID-19 and rarely last for more than 12 weeks.

4. Endocrine manifestations

It is well known that fasting glucose levels in COVID-19 patients are significantly higher than in patients with bacterial pneumonia, both in patients with and without DM [50]. Mechanisms of carbohydrate metabolism in COVID-19 patients are versatile and include virus affinity with pancreatic endocrine cells [51], insulin resistance caused by systemic pro-inflammatory reaction due to cytokine storm [52] and management of COVID-19 infection. A large cohort study (47,780 COVID-19 survivors) in England showed that DM after NCVI was diagnosed in 4.9 % of respondents [53].

In their study, Ruggeri RM et al. described a case study of a woman who developed subacute thyroiditis with thyrotoxicosis six weeks after SARS-COV-2 onset [54]. In a study of a large cohort of patients to identify persistent changes in thyroid gland functions after recovery from COVID-19, Bernard Khoo et al. found that, on the average during 79 days of follow-up, two patients were diagnosed with subclinical hypothyroidism, 4 patients had secondary hypothyroidism and 2 patients developed subclinical hypothyroidism without any prior thyroid disorders [55].

5. Neurological manifestations

A meta-analysis to study the incidence of long COVID-19 symptoms, which included 7 studies (47,910 patients aged 17 to 87 years), demonstrated that the most common symptoms were fatigue (58 %), headache (44 %) and poor concentration (27 %) [56].

A large meta-analysis of persistent neurological manifestations in 9,944 patients reports that the most common symptom in patients with a history of COVID-19 infection was fatigue (52.8 %); then cognitive disorders (35.4 %); paresthesia (33.3 %); sleep disorders (32.9 %); and dizziness (26.4 %) [57].

During examination of patients 4 weeks after recovery and a negative COVID-19 PCR test, the most common symptom reported by patients was fatigue 84.8 % (n = 420). The incidence of this symptom in 12 weeks was 82.9 % (n = 295) [58].

In their article, Rudroff T et al. define post-COVID-19 fatigue as reduced physical and/or mental capacity as a result of changes in central, psychological and/or peripheral mechanisms caused by COVID-19 [59].

In ICD-10, this PCS manifestation is included in G93.3 Postviral Fatigue Syndrome.

Data from a cohort study of outpatient patients (n = 458) showed a high incidence (46 %) of persistent feeling of tiredness 4 months after recovery, when Chalder Fatigue Scale (CFQ-11) was used [60]. Also, this scale was used to analyse the incidence of this symptom in a study of 128 subjects (49.5 ± 15 years old; 54 % were females), where a majority of patients reported persistent fatigue (67 subjects, 52.3 %) on the average 10 weeks after first symptoms of COVID-19 [61].

Halpin S et al. found out that fatigue after discharge (4–8 weeks later) was reported by 72 % of patients who were treated in ICU during the acute phase, and by 60.3 % of subjects who were treated in the therapeutic unit [35].

As evident from results of numerous studies, the most common and persistent signs of PCS, in addition to asthenia, are cognitive disorders, primarily poor attention and concentration, mental block.

In a study conducted at the State Budgetary Healthcare Institution of the Novosibirsk Region State Novosibirsk Regional Clinical Hospital to characterise neurological variants of PCS (neurology patients with a history of confirmed COVID-19), toxic and metabolic encephalopathy was prevailing — 412 subjects out of 455. This pathology manifested primarily with confused and depressed consciousness in 211 subjects (51.2 %), cognitive disorders (moderate cognitive disorders, dementia) in 201 subjects (48.8 %). Also, there was a case of a cerebrovascular pathology in the form of acute cerebrovascular accident (ischaemic type) in a 36-year-old woman without any history of vascular risk factors [62].

In an examination of a Spanish cohort during 6 months after discharge from the hospital after COVID-19, neurological manifestations were recorded in 20.8 % of cases. The most common symptoms were persistent anosmia and dysgeusia (7.2 %), headache (5.3 %), confused consciousness (2.6 %). 3.4 % of subjects had symptoms of paresthesia and tremor [63].

A prospective Italian study showed that one year after COVID-19, 22.0 % of subjects reported deterioration of olfaction or taste (67 patients out of 161) [64].

Out of 356 persons who reported persistent symptoms of COVID-19 12 weeks after diagnosis, 12 (3.4 %) patients noted loss of taste, 8 (2.2 %) patients — persistent headache, 18 (5.1 %) patients — anosmia [58].

The data from SF-36 quality of life questionnaire in a study by Arnold DT demonstrate low values both for physical and mental health after NCVI [65].

In a study by van den Borst, all SF-36 scores were reduced, especially physical and general health. Also, the Hospital Anxiety and Depression Scale (HADS) demonstrated abnormal values in 10 % and 12 % of subjects for respective parameters [66].

Deteriorated quality of life was recorded in 44.1 % of patients on EQ–5D scale, on the average 60.3 days after the first symptom of COVID-19 [67]. The most common symptoms in patients with PCS were anosmia, loss of taste and fatigue, when patients were observed 4 and 7 months after onset of COVID-19 symptoms [68].

6. Mental and behavioural disorders

In a study by Romero-Duarte Á. et al., the incidence of symptoms of mental disorders was 12.2 % after hospitalisation for COVID-19. The scientists recorded a high incidence of anxiety (6.8 %), sleep disorders (4.9 %) and symptoms of depression (4.4 %), primarily in women [63]. Similar data were reported in a Chinese study: sleep disorders were recorded in 26 % (437 subjects out of 1,655), anxiety or depression were recorded in 23 % of patients [30].

A large meta-analysis of the incidence of mental changes during the post-COVID period, which included 66 articles (3 to 266,586 subjects), demonstrated that 40 studies reported anxiety and/or depression, 20 studies — PTSD symptoms, 27 studies — cognitive deficit, 32 — fatigue during observation, and 23 studies reported sleep disorders. The identified risk factors were the severity, duration of symptoms and female sex [69].

7. Changes in other organs and systems

In a study by Romero-Duarte Á. et al., the most common symptom was exanthematous disease (3.1 %). High incidence of alopecia (3.0 %), especially in women, is of special interest [63]. In an article by Augustin M. et al., 9 patients (2.5 %) out of 353 reported alopecia after 7 months of follow-up [68].

35 days after discharge from hospital after COVID-19, 51 % of respondents reported permanent muscle pain [36]. According to guidelines developed by the Russian Scientific Medical Society of General Practitioners, "Features of long-COVID infection. Therapy and rehabilitation", post-COVID arthritis is diagnosed in 22.6 % of COVID-19 survivors, where articular syndrome is easily arrested with non-steroidal anti-inflammatory drugs. In patients with undifferentiated arthritis, rheumatoid disease was verified in 49 % of cases during 3–6 months (undifferentiated arthritis with antinuclear antibodies — 10 cases (26.3 %), Sjogren disease — 2 cases (5.2 %), systemic lupus erythematosus — 1 case (2.6 %), unspecified autoimmune disease — 1 case (2.6 %), rheumatoid arthritis — 2 cases (5.2 %), undifferentiated arthritis — 2 cases (5.2 %)) [5].

Results of available studies demonstrate long-lasting haemostasis changes after NCVI. However, currently, the clear pathogenesis of changes in these parameters is unknown. Several papers described increased D-dimer, C-reactive protein, ferritin in post-COVID period [70,71,72].

Artemyeva G. A. et al. examined 100 COVID-19 convalescents (55 patients 70–116 days (median: 99) after hospitalisation, 45 patients — 139–173 days (median: 160)). 37 subjects were controls. All patients underwent coagulation testing, aggregometry, thrombodynamics examination and clot dissolution test. Results demonstrated that 2–6 months after disease, patients had normalised clotting parameters, but clot dissolution was excessively activated [73]. In their study, Liam Townsend et al. found out that increased D-dimer levels persisted 2 months after recovery from acute COVID-19 infection and were observed in a cohort of predominantly young patients [70]. Venturelli S et al, reported several cases of pulmonary artery thromboembolia, with D-dimer levels of over 2,000 ng/mL, 80 days after discharge from the hospital after COVID-19 [74]. However, it is worth mentioning that studies of clinical manifestations of post-COVID clotting disorders are very few; they are limited to the number of observations and usually last maximum for a month after acute COVID-19 period. In their systematic review, Nalbandian A et al. assumed that the incidence of post-COVID venous thromboembolism was less than 5 % [75].

In addition, a number of studies report a long-lasting increase in blood cytokines, such as interleukin-6,

Table 1. *Characteristics of the severity of post-COVID syndrome*

System	Postcovid syndrome of mild severity	Postcovid syndrome of moderate severity
Cardiovascular system [16-29]	Non-physiological sinus tachycardia	De novo development/decompensation: – Coronary heart disease, including the development of myocardial infarction in the acute and post-acute period of COVID-19 – AF – CHF
	Elevation of high-sensitivity troponin T without myocardial infarction clinic	
	Post-COVID tachycardia syndrome (POTS, inadequate sinus tachycardia)	
	De novo development/aggravation of hypertension	
Bronchopulmonary system [5, 20, 30-39]	CT changes (not affecting quality of life)	CT changes affecting quality of life with a predominance of restrictive disorders according to spirometry
	Spirometry changes (not affecting quality of life)	Development of reversible and irreversible bronchial obstruction
	Dyspnea grade 0-1 (mMRC)	Dyspnea grade 2-5 (mMRC)
	Chronic cough	Development of interstitial lung disease
Gastrointestinal manifestations [40-49]	Abdominal pain	Exacerbation of the course of chronic diseases: – Gastroesophageal reflux disease – Peptic ulcer disease – Irritable bowel syndrome – Exacerbation of diseases of the hepatobiliary system
	Diarrhea/constipation	
	Functional dyspepsia syndrome	
		Drug-induced liver injury
Endocrinological manifestations [50-55]	Prediabetes	De novo development/decompensation of DM
		Subacute thyroiditis
	Subclinical hypothyroidism	Manifest hypothyroidism
		Subclinical Hyperthyroidism and Manifest Thyrotoxicosis
Neurological manifestations [35, 56-68]	Fatigue syndrome after a viral infection	Acute cerebrovascular accident and/or transient ischemic attack in the acute and post-acute periods of COVID-19.
	Paresthesias	
	Tremor	
	Vertigo	
	Cognitive disorders (attention disorders and decreased concentration, a feeling of «brain fog»)	
	Parosmia	Long-term persistent anosmia/dysgeusia
	Headache	
Mental and behavioral disorders [30, 63, 66, 69]	Development of subclinical anxiety/depression (HADS score 8-10, Spielberger scale less than 45)	Development of clinically significant anxiety/depression (HADS score of 11 or more, Spielberger scale greater than 45 points)
	Sleep disorders	Development of PTSD
Changes in other organs and systems [5, 36, 63, 68, 70-77]	Exanthema	Alopecia
	Muscle pain	Development of de novo rheumatological diseases.
	Disorders in the hemostasis system without clinical manifestations and with a low probability of thrombosis (IMPROVEDD score <2 points)	High risk of thromboembolic complications (IMPROVEDD score ≥2 points)

Note: AF — atrial fibrillation, CHF — chronic heart failure, hypertension — arterial hypertension, CT — computed tomography of the chest, PTSD — post-traumatic stress disorder, DM — diabetes mellitus

tumour necrosis factor alpha, nerve cell growth factor, etc. [76, 77]. However, this data are mostly fundamental, since routine clinical testing of these biomarkers is very expensive.

Hence, it can be concluded that identification of PCS severity is advisable not only in terms of classification and consolidation of available information, but also for the development of preventive and therapeutic measures. Taken analysed, available studies, it is assumed that PCS division into two severity stages is the most rational: mild PCS (development of potentially reversible conditions) and moderate PCS (development of a chronic condition or aggravation of a pre-existing disease). The impact of symptoms on the quality of patient's life should be taken into account as well. For instance, severe anxiety disorder has a more negative impact on the quality of patient's life than mild depression; even marked fibrous changes in lungs seen on CT not always impact the quality of life in some patients, but cause significant restrictive ventilation disorders in other persons.

Proposed PCS characteristics depending on severity are presented in Table 1.

Conclusion

Summing up the analysed data from available studies evaluating PCS in patients who had laboratory confirmed NCVI, at least 1 month after recovery, two stages of PCS severity were identified depending on the presence of identified signs, symptoms, newly diagnosed diseases and decompensation of pre-existing conditions (Table 1).

We believe that the presence and severity of PCS will depend on the presence of at least one sign from Table 1, which develops during or after verified COVID-19 infection and persists for over 4 weeks from disease onset; provided that it cannot be attributed to other reasons.

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ЭПИДЕМИОЛОГИЯ, КЛИНИЧЕСКИЕ ОСОБЕННОСТИ И ТАКТИКА ЛЕЧЕНИЯ АРТЕРИАЛЬНОЙ ГИПЕРТОНИИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА. ОБЗОР ЛИТЕРАТУРЫ

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Epidemiology and Clinical Features of Arterial Hypertension in Patients with Type 2 Diabetes Mellitus. Literature Review

Резюме

Артериальная гипертония и сахарный диабет 2 типа часто сочетаются и взаимно усиливают неблагоприятное влияние на сосудистый и почечный прогноз. Артериальная гипертония представлена примерно у 50 % больных с сахарным диабетом 2 типа, а диабет в свою очередь выявляется приблизительно у 20 % лиц с артериальной гипертонией. Риск развития артериальной гипертонии у больных с сахарным диабетом 2 типа в 2-2,5 раза выше, чем у лиц без диабета; во столько же раз наличие артериальной гипертонии увеличивает риск формирования сахарного диабета 2 типа. Артериальная гипертония и диабет взаимно отягощают течение друг друга: с одной стороны, наличие артериальной гипертонии существенно увеличивает вероятность развития диабетических макро- и микрососудистых осложнений (включая диабетические нефропатию и ретинопатию); с другой стороны, сахарный диабет 2 типа, как классический независимый фактор сердечно-сосудистого риска, примерно в 2 раза повышает риск осложнений, присущих артериальной гипертонии. Тщательное лечение диабета с поддержанием целевых значений гликемии в течение длительного времени может быть ассоциировано со снижением вероятности развития артериальной гипертонии на 24 % в сравнении с менее адекватным контролем гликемии. Артериальная гипертония при сахарном диабете 2 типа может иметь ряд особенностей, которые отличают таких больных от общей популяции лиц с артериальной гипертонией. К таким особенностям относятся: более высокий удельный вес изолированной систолической артериальной гипертонии и резистентной артериальной гипертонии, определенных типов нарушений циркадного ритма артериального давления (категорий «non-dipper» и «night-peaker»); частое сочетание с альбуминурией; нередкие высокая солечувствительность и объем-зависимый характер артериальной гипертонии и другие.

Ключевые слова: *сахарный диабет 2 типа, артериальная гипертония, изолированная систолическая артериальная гипертония, резистентная артериальная гипертония*

Конфликт интересов

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

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Abstract

Hypertension and type 2 diabetes mellitus are often combined and mutually enhance the adverse effect on vascular and renal prognosis. Hypertension is present in about 50 % of patients with type 2 diabetes, and diabetes, in turn, is detected in about 20 % of people with hypertension. The risk of developing hypertension in patients with type 2 diabetes is 2-2.5 times higher than in people without diabetes; the presence of hypertension increases the risk of type 2 diabetes by the same number of times. Hypertension and diabetes mutually burden each other: on the one hand, the presence of hypertension significantly increases the likelihood of developing diabetic macro- and microvascular complications (including diabetic nephropathy and retinopathy); on the other hand, type 2 diabetes, as a classic independent cardiovascular risk factor, increases the risk of complications inherent in hypertension by about 2 times Careful treatment of diabetes with maintenance of target values of glycemia for a long time may be associated with a decrease in the likelihood of developing hypertension by 24 % compared with less adequate control of glycemia. Hypertension in type 2 diabetes may have a number of features that distinguish such patients from the general population of people with hypertension. Such features include a higher proportion of isolated systolic hypertension and resistant hypertension, certain types of circadian rhythm disorders of blood pressure (categories "non-dipper" and "night-peaker"), frequent combination with albuminuria, frequent high salt sensitivity and volume-dependent nature of hypertension, and others.

Key words: *type 2 diabetes mellitus, arterial hypertension, isolated systolic arterial hypertension, resistant arterial hypertension*

Conflict of interests

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α-AB — alpha-adrenoblocker, β-AB — beta-adrenoblocker, AH — arterial hypertension, BP — blood pressure, CAN — cardiovascular autonomic neuropathy, MRA — mineralocorticoid receptor antagonist, GLP1ra — glucagon-like peptide-1-receptor agonist, ASA — acetylsalicylic acid, CCB — calcium channel blocker, DBP — diastolic blood pressure, DNP — diabetic nephropathy, ACE inhibitors — angiotensin-converting enzyme inhibitors, IHD — ischemic heart disease, iSGLT2 — sodium glucose linked co-transporter-2 inhibitors, ISAT — isolated systolic arterial hypertension, LV — left ventricle, RATS — renin-angiotensin system, RCT — randomised controlled study, SBP — systolic blood pressure, DM — diabetes mellitus, GFR — glomerular filtration rate, CVR — cardiovascular risk, CKD — chronic kidney disease, LDL-C — low density lipoprotein cholesterol, CCF — chronic cardiac failure

Relevance

Cardiovascular disorders are a leading cause of deaths in patients with type 2 diabetes mellitus (DM) [1]. One of the most common and significant cardiovascular diabetes-associated risk factors is arterial hypertension (AH) [2]. In type 2 DM, cardiovascular risk factors are often observed in various combinations; usually, AH is combined with abdominal obesity, dyslipidemia, albuminuria, blood-clotting disorders [3]. Such risk factor associations in type 2 DM patients and also in individuals with metabolic syndrome significantly and mutually boost adverse effects, promoting development and progression of a number of macro- and microvascular complications [4].

AH is a serious open problem in the current clinical picture of internal diseases, because of its high incidence and significant adverse effect on the prognosis. AH is recorded in 30–45 % of the general adult population. Its incidence grows with the age, and at least 60 % of individuals of over 60–65 years of age have high blood pressure (BP) or take antihypertensives. According to epidemiological studies, the probability of AH developing at a later stage in life in young adults of 20–40 years old can be as high as 90–95 % [2, 5].

AH is associated with a high incidence of cardiovascular death and a higher risk of cardiovascular complications in all age groups. There is also independent correlation between AH and a risk of cardiac failure, peripheral artery involvement and impaired renal function [3, 6, 7].

Systolic BP (SBP) values demonstrate the closest correlation with an increase in cardiovascular risk. This is particularly true for individuals over 50 years of age. SBP values tend to increase throughout life; at the same time, diastolic BP (DPB) starts decreasing at the age of 50–60 years [8, 9]. The process of SBP increase and DBP decrease (with an increase in pulse pressure) shows a progressive increase in vessel wall stiffness in the arterial bed. The exact mechanisms of this process are still understudied. It is worth mentioning that higher SBP values in elderly people are the most significant independent risk factor of cardiovascular and cerebrovascular complications, as well as renal disorder progression.

In individuals below 50 years old, DBP values demonstrate the most clear correlation with the degree of cardiovascular risk [2, 4, 9].

Despite modern diagnostic and therapeutic methods, the progress of AH therapy is modest: in a number of countries, far fewer than a half of all patients with AH manage to control their AH within the target range. Epidemiological data show that approx. 50 % of AH patients in Western Europe are unaware of their higher AH (i.e. they are not diagnosed with AH); among individuals with AH, just 10–15 % have satisfactory AH control [1, 6, 9].

Type 2 DM is a chronic metabolic disorder associated with progressive reduction in adequate insulin secretion by β-cells of pancreatic islets, usually as a result of insulin resistance. Type 2 DM is a prevailing form of DM globally, accounting for 90–95 % of all cases of diabetes [1, 8, 10].

This review presents results of analysis of 2010–2023 literature in PubMed, RSCI (Russian Science Citation Index), Scopus. The following keywords were used: arterial hypertension, type 2 diabetes mellitus, isolated systolic arterial hypertension, resistant arterial hypertension. The analysis includes the data of the authors conducting clinical trials to identify specific pathogenesis, clinical manifestations and management of patients with arterial hypertension and type 2 diabetes mellitus.

Epidemiology

The International Diabetes Federation (IDF) regularly publishes epidemiological DM evaluations and prognosis; the last report was presented in 2023. There are some data from the report. According to expert IDF evaluations, in 2019, approximately 463 mln. people all over the world had diabetes (i.e. 9.3 % of all world population, of which approx. 462 mln. people had type 2 DM). It is expected that by 2030 the number of DM patients globally will reach 578 mln. (10.2 % of the world population), while by 2045 — 700 mln. (10.9 %) [4, 11,12].

According to experts, nearly a half of 463 mln. of DM patients are unaware of their condition. DM unawareness in high-income nations is 38.5 %, in average-income countries — 52.6 %, while in low-income states — 66.8 %. On top of that, 374 mln. people worldwide (7.5 % of the global population) have impaired glucose tolerance; by 2030, this number will reach approx. 54 mln. people (8.0 %), by 2045 — 548 mln. (8.6 %) [4, 11, 12].

In the Russian Federation, the number of people with confirmed DM is nearly 4.58 mln. (3.1 % of the population). It is assumed that approximately the same number of people have an undiagnosed disease; therefore, there are significant shortages in medical treatment [11].

Prognosis

Type 2 DM is associated with a high incidence of severe, debilitating complications; it significantly contributes to mortality rates. In Eastern countries, diabetes is the leading cause of blindness; it accounts for up to 40 % of all terminal renal failure cases. A risk of myocardial infarction and cerebral stroke in type 2 DM patients is assumed to be 2–4 times higher than in individuals of the same age and sex, but having no diabetes. The incidence of low limb amputation in type 2 DM is approx. 20 (!) times higher than in individuals without diabetes. Type 2 DM reduces the life expectancy by approx. 10 years; this value is even higher with disease onset before the age of 55 years [11,12,13, 14].

AH and type 2 DM are often comorbidities and mutually enhance their adverse effects on vascular and renal prognosis. It is assumed that approx. 50 % of type 2 DM patients have AH; at the same time, approx. 20 % of AH patients have diabetes. In a recent register, patients with type 2 DM had BP of over 140/90 mm Hg or were continuously taking antihypertensives in 71 % of cases. The risk of AH in patients with type 2 DM is 2–2.5 times higher than in individuals without diabetes; and AH increases the risk of type 2 DM by 2–2.5 times. AH and diabetes mutually aggravate the course of disease: AH significantly increases the probability of diabetic macro- and microvascular complications (including diabetic nephropathy (DNP) and retinopathy); type 2 DM, being a classic independent cardiovascular factor, causes a 2-fold increase in the rate of AH-associated complications. Of importance is the information that accurate diabetes management, which ensures long-term target glycaemia values, can be associated with reduction in the probability of AH by 24 % vs. less adequate glycaemia control [5, 9, 12, 15].

Morbid Physiology

High rates of the combination of type 2 DM and AH are a result of the similarity in a number of pathological mechanisms of these conditions. These include insulin resistance, dyslipidemia, activation of proinflammatory and prothrombotic factors, endothelial dysfunction, impaired vascular tone regulation, high salt sensitivity,

impaired sodium excretion by kidneys, etc. In patients with essential AH, the rate of insulin resistance is as high as 50 %, and individuals with such a combination have 2–3-fold increase in the cardiovascular risk severity (when using SCORE, a common European scale). It has been found that the rate of insulinemia in AH demonstrates direct correlation with BP values, and a number of specialists can treat essential AH as an insulin-resistant condition. In turn, very often higher insulin levels, observed with insulin resistance (in individuals with type 2 DM, pre-diabetes, impaired glucose tolerance), can affect insulin-sensitive tissues (e.g. kidneys) and promote AH development (e.g. promoting sodium and water retention in kidneys). It is also assumed that AH and insulin resistance can have a common genetic base. This concept is based on a higher incidence of impaired glycaemic balance in normotensive descendants of AH patients vs. children of individuals without AH [7, 10, 13, 16].

Literature sources discuss the characteristics of AH in type 2 DM patients. Points of view regarding this issue are versatile. A number of specialists emphasise that the pattern of AH in these individuals is close to the pattern in individuals without diabetes, and there are no special features. At the same time, other researchers point out to a number of aspects, which can distinguish patients with AH and type 2 DM from the general AH population.

The most typical characteristics of a combination of AH and type 2 DM:

- Salt sensitivity predisposition (so AH is often volume-dependant)
- Impaired circadian BP rhythm (with an increase in the relative weight of "non-dipper" and "night-peaker" categories)
- Isolated systolic AH
- Resistant AH
- Albuminuria
- Orthostatic hypotonia.

Currently, all these features are considered to be independent cardiovascular risk factors. Besides, their presence can impact AH management. For instance, in volume-dependent AH, the use of thiazid-like diuretics is justified, while individuals with albuminuria should take angiotensin-converting enzyme inhibitors (ACE inhibitors) or sartans for kidney protection. These possible characteristics of AH in type 2 DM are detailed below [5, 8, 10, 17].

Clinical Profile and Management of the Key Pathophysiological Characteristics of AH and Type 2 DM

Salt sensitivity

Higher salt sensitivity is typical of some categories of AH patients, including elderly patients, patients with DM, obesity, impaired renal function, low renin plasma activity. Also, higher salt sensitivity is observed in African Americans.

The mechanism of higher salt sensitivity in type 2 DM patients is still unclear. Salt sensitivity can be genetic and can be associated with hereditary reduction in the number of functional nephrons (normally, each kidney has approx. 1 mln. of nephrons), impairing the renal ability to excrete sodium and water. In this category, AH tends to rise in case of excessive consumption of sodium chloride and water; in such cases, AH demonstrates good response to dietary reduction of sodium chloride and the use of diuretics. In type 2 DM, thiazid-like diuretics (indapamide, chlortalidone) are preferable due to their metabolic neutrality and marked organ-protective properties. Thiazids (e.g. hypothiazid) are less preferable due to possible adverse effect for glucose profile (however, internationally recognised experts think they can be used also in DM patients, if thiazid-like products are unavailable). In case of impaired renal function (especially where glomerular filtration rate (GFR) is below 30–60 mL/min), loop diuretics are recommended as a component of antihypertensive therapy.

Taking into account their possible higher salt sensitivity, individuals with AH and type 2 DM may benefit from a new class of antihyperglycemic drugs — *sodium glucose linked co-transporter-2 inhibitors* (iSGLT2). In a number of large randomised controlled trials (RCTs), these drugs demonstrated a variety of organ-protective properties and the ability to improve cardiovascular and renal prognosis in type 2 DM patients (especially in chronic cardiac failure (CCF) and DNP). A significant advantage of these drugs in patients with AH and type 2 DM is their ability to enhance sodium excretion, thus, they also have marked antihypertensive effect. It is worth to discuss the mechanism of iSGLT2 action in detail [9, 13, 18].

These drugs affect sodium glucose linked co-transporter-2, which is a glucose transport protein located in the anterior part of proximal tubules of nephrons; its function is to re-absorb 80–90 % of glucose from

primary urine. Glucose is transported via tubule cell membranes from tubule opening using sodium gradient. Increased diuresis with the use of iSGLT2 is associated with osmotic effect of glucosuria and natriuresis. According to some authors, this drug effect is extremely significant and is one of the most important favourable mechanisms of iSGLT2 in CCF. It has been demonstrated that iSGLT2 can potentiate the effect of loop diuretics in CCF. It is assumed that the use of iSGLT2 is associated with a less marked rate (as compared with loop and thiazide diuretics) of reflective neurohumoral activation. Natriuretic and diuretic effects of these drugs are associated with hypotensive effect. The degree of this effect caused by iSGLT2 is clear (it can be compared with the effect of thiazide diuretics, beta-adrenoblockers (β-AB) and calcium channel blockers (CCBs), and, according to some sources, is even superior). Although the current AH therapy recommendations do not include iSGLT2 as antihypertensives, some competent experts have already put forward such proposals. Of note, this class of drugs has been included in the revised recommendations not only for type 2 DM management, but also for CCF with low, intermediate and preserved left ventricle (LV) ejection fraction (both with and without diabetes), as well as for chronic kidney disease (CKD) (including DNP and non-diabetic glomerulopathy). To conclude the discussion of the possibilities of iSGLT2, we would like to emphasise their versatile additional organ-protective and pleiotropic effects: antiinflammatory action, reduction of oxidative stress and sympathetic tone, improved vasodilation, improved energy metabolism by myocardium, reduced cardiac remodeling, reduced ischemic and reperfusion myocardial injury, reduced uricemia, better autophagy and lysosomal degradation, reduced body weight [15,18].

Impaired circadian BP rhythm

Normally, during 24-hour BP monitoring, it is higher during daytime, while at night it reduces by 10–15 % vs. daytime values (dipper). A lesser reduction in BP values at night (less than < 10 % of daytime values) is called non-dipper, while higher nocturnal BP values are called night-peaker. Two latter circadian BP rhythms are pathologic. According to a number of articles. they are more common in patients with AH and type 2 DM than in AH alone; other authors suggest absence of any relation between abnormal circadian BP rhythms and type 2 DM. It is known that impaired circadian BP rhythm is associated with a higher risk of cardiovascular death irrespective of sex, age, body mass index, smoking status, and a history of cardiovascular disorders. In a number of epidemiological studies, nocturnal BP values were more reliable predictors of all cause mortality in AH than daytime BP values or BP measured at a visit to the doctor. The causes of more frequently reported circadian BP rhythm abnormalities in individuals with AH and type 2 DM vs. patients with AH alone are still not clear [12,19,20].

To correct such *circadian BP rhythm abnormalities,* the patient should take at least some antihypertensive before bed [12,19,20].

Resistant AH

This term is used for cases when BP values remain outside the target range, despite the fact that the patient follows recommendations for lifestyle changes (including reduced consumption of sodium chloride) and takes full doses of 3 classes of compatible antihypertensives, with one of these 3 classes being a diuretic. The incidence of resistant AH (according to some US registers) is approx. 9 %. Causes of resistant AH are versatile and include poor compliance, presence of symptomatic AH (e.g. renoparenchymal, renovascular, endocrine, etc.); resistant AH is more common in obese and elderly patients, as well as (potentially) in type 2 DM patients. The mechanisms of a higher incidence of resistant AH in diabetes are unclear; endothelial function and insulin resistance are discussed among other causes.

In order to overcome AH resistance to therapy, the following measures are recommended: thorough review of patient's compliance to therapy and correction where necessary, ruling out symptomatic nature of AH (in case of subclinical hyperaldosteronism, it is essential to use mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone); wider use of 4–5 and more components in the therapy regimen (for instance, CCBs, thiazid or thiazid-like diuretic, ACEi or sartan, MRA, possible combined with a central-action drug, β-AB, alpha-adrenoblocker (α-AB), etc.). The role of complex multicomponent combinations of antihypertensives in such patients, their beneficial effect and safety are difficult to assess. Recently, resistant AH therapy has included some invasive procedures (catheter-based renal denervation, implantation of devices which activate carotid adrenergic receptors, etc.) [21,22].

Considering the important role played by *occult hyperaldosteronism* in resistant AH development, and the significance of MRAs in the elimination of AH resistance to therapy, we will briefly discuss their possible use in AH, including individuals with type 2 DM. Until recently, these drugs were used mainly in the management of CCF cases with low LV ejection

fraction and in post-infarction patients. Currently, they are widely used in the combined therapy of AH as a fourth drug (as an addition to traditional three-component combinations of ACE inhibitor or sartan, thiazide/thiazide-like diuretic and CCB). Spironolactone is a non-selective drug; in AH therapy, it is usually used in low, sub-diuretic doses (25–50 mg/day). The use of low doses makes it possible to minimise such adverse events as gynecomastia, decreased interest and painful menstruation. Drugs of this class are effective in reduction of BP values both in a combination with other classes of drugs and as monotherapy; however, spironolactone is superior to eplerenone in management of high BP. In a recent study PATHWAY-2 (335 participants, of which 46 individuals with type 2 DM), spironolactone 25–50 mg/day was added to a three-component combined antihypertensive therapy with ACE inhibitor (or sartan), CCB and diuretic, as compared to doxazosin and bisoprolol, and demonstrated a more prominent antihypertensive effect without any events of gynecomastia, hyperkalemia and impaired renal function. The effect and tolerability in type 2 DM patients were comparable to the effect and tolerability in non-diabetic individuals. The organ-protective effect of spironolactone is associated with LV hypertrophy regression, antifibrotic effects in myocardium and, possibly, in vascular walls, as well as with reduced microalbuminuria rates [21,22].

Isolated systolic AH

This term is used for a situation when SBP values rise above 140 mm Hg without any increase in DBP, the values of which remain below 90 mm Hg. The majority of world experts consider isolated systolic AH (ISAH) to be an isolated pathology, typically observed in elderly people and associated with lower artery wall flexibility [23]. Higher SBP values are an important pathophysiological factor, contributing to LV hypertrophy; reduced DBP can result in poor coronary blood flow. The incidence of ISAH rises with age; in elderly people, it is the most common form of AH (according to Western specialist, it can account for 80–90 % of all AH cases in patients of 65 and over years of age) [24]. In elderly individuals, ISAH is associated with a significantly higher cardiovascular risk as compared to systolic-diastolic AH (with comparable SBP values) [19]. In order to assess the rate of an additional cardiovascular risk in ISAH, it is recommended to use the same SBP values, the same nomenclature for risk factors, target organ involvement and comorbidities, as in systolic-diastolic AH. At the same time, experts believe that extremely low DBP values (60–70 mm Hg and below) are associated with additional increase in the risk [16].

The mechanism of correlation between ISAH and type 2 DM has been understudied; it is true both for epidemiology, pathogenesis and management strategies. Considering that a lot of type 2 DM patients are elderly people, it is naturally to expect a high incidence exactly of this AH form; however, reliable epidemiological data in this regard are lacking. Since age-associated rigidity of aortic and large vessel walls is the leading cause of ISAH development, essential is the information that diabetes-associated metabolic disorders can contribute to poor vascular wall flexibility. Endothelial dysfunction, activation of local and system pro-inflammatory and profibrotic mechanisms are essential, since they are closely associated with insulin resistance, glucotoxicity, lipotoxicity and accumulation of glycation products in tissues. Reduced elasticity and damping capabilities of vascular walls are facilitated by typically early onset of type 2 DM and faster progression of atherosclerotic changes in vascular walls. An increase in systolic blood velocity resulting from higher SBP and lower DBP (as damping capabilities weaken) caused by higher vascular wall rigidity, lead to a higher pulse BP, higher mechanical load over the vascular wall with an increase in shear stress. All this contributes to the progression of vascular damage and facilitates further increase in cardiovascular risk. Of note, in type 2 DM patients, ISAH develops in younger age as compared to non-diabetic population. At the same time, it is worth mentioning that AH in middle-aged type 2 DM patients is systolic-diastolic (both SBP and DBP values rise) [7, 19, 23].

ISAH therapy includes standard classes of hypotensives; diuretics and CCBs are preferable [11,12].

Albuminuria

Being a marker of renal damage, albuminuria is diagnosed more often in patients with AH and type 2 DM as compared to non-diabetic AH patients. Currently, the term "microalbuminuria" is outdated; in nephrology literature, this term has been replaced with albuminuria, however, the former is still used in clinical practice. Most often, albuminuria in this population is a sign of a diabetes-specific kidney damage — DNP (where glomeruli are involved most of all in the form of nodular glomerular sclerosis). Clinical manifestations of DNP usually appear 10–15 years after onset of diabetes (in type 2 DM patients, identification of this particular moment is challenging, therefore, in real time practice, this period can be significantly shorter). In type 2 DM, albuminuria, as a sign of DNP, is diagnosed in 14–20 % of cases and

often precedes AH development. It is worth noting that, if diagnosed early, albuminuria in type 2 DM patients can be reversed with the use of modern efficient kidney-protective approaches [12,25].

In developed countries, *diabetic nephropathy* is a leading cause of end stage renal disease; in dialysis patients, its share is 40 %. A very important factor in kidney damage progression in type 2 DM patients is AH. High BP values contribute both to albuminuria aggravation and its progression to proteinuria (> 0.3 g/day, then > 1.0 g/day, with possible development of nephrosis and gradual reduction in renal function) [16,20,25].

The initial stage of DNP (glomerular hyperfiltration) is asymptomatic (no albuminuria is recorded). Later, higher GFR levels drop to normal values, and albumin excretion with urine rises (albuminuria starts developing). Then, manifest DNP appears: minimal proteinuria progresses to severe condition (in this case, it is nephrosis); microscopic hematuria, cylindruria are also possible; AH appears or aggravates. GFR gradually drops, up to marked and severe kidney failure (stage 3–5 CKD). The clinical pattern (especially in type 2 DM) often presents with various cardiovascular complications, typical of diabetes in general and DNP in particular: ischemic heart disease (IHD), rhythm disturbances, CCF, and other macro- and microvascular diabetic complications [23,25].

Efficient management of AH in type 2 DM patients is based on a pivotal approach to kidney protection, which insures minimisation of the rate of renal damage both at early and later stages, as well as when the renal function is impaired. The most evidence-based hypertensives are renin-angiotensin system (RATS) blockers, such as ACE inhibitors or sartans [12,25]. In individuals with DNP and AH, achievement and maintenance of target AH values are associated with reduction in cardiovascular risk, as well as reduced rate of renal damage progression. Prescription of hypertensives in addition to life-style changes is recommended in DNP patients if their AH levels are ≥ 140/90 mm Hg (for patients of over 80 years of age — ≥ 160/90 mm Hg). Target values for such individuals are SBP of 120–129 mm Hg, DBP — 70–79 mm Hg (for individuals of over 65 years of age — systolic BP of 130–139 mm Hg). First-line antihypertensives for patients with DNP and DM are ACE inhibitors or sartans, supplemented with CCBs and/or thiazid/thiazid-like diuretics. Where necessary, the following drugs can be used in addition to the above-mentioned drugs: 1) loop diuretics (especially with GFR of 45 mL/min/1.73 m^2); 6) nitrates (in elderly patients, with IHD). During therapy, it is recommended to continuously control proteinuria, electrolyte levels and serum creatinine, GFR values [17,19,25]. The general approach to DNP management is presented in Figure 1.

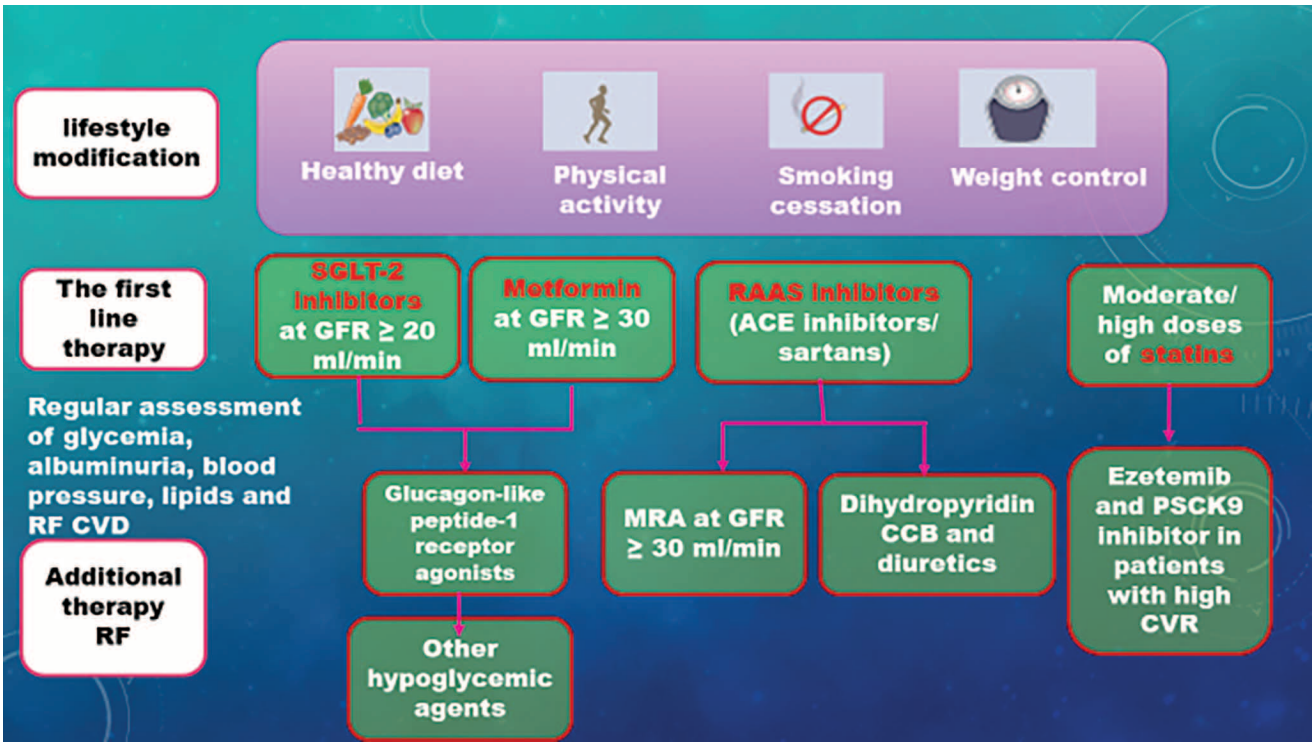

Figure 1. *General view on the management of patients with DNP*
Note: RF — risk factors; CVD — cardiovascular diseases; CVR — cardiovascular risk; PCSK9 — proprotein convertase subtilisin-kexin type 9

Orthostatic hypotonia

This term is used to describe episodes of rapid SBP reduction by ≥ 20 mm Hg or DBP by ≥ 10 mm Hg during 3 minutes after verticalisation from sitting or supine position; it is often associated with compensatory tachycardia. The incidence of orthostatic hypotonia rises with age; in elderly patients, it can reach 5–30 %. Orthostatic hypotonia is associated with a higher risk of falls and fractures [5, 16].

In quick rising, approx. 10 % of the circulating blood volume goes from chest organs to lower body vessels. Normally, BP reduction is prevented by neurohumoral system activation and changes in pressure receptor function. With age, the degree of such activation declines, thus causing lower BP during rising. Progressive orthostatic hypotonia in elderly people is characterised by slow reduction in SBP when rising (and compensatory growth in heart rate). Symptoms usually appear several minutes later. Type 2 DM patients may have episodes of orthostatic hypotonia more often than non-diabetic individuals. They are facilitated by diabetes-induced vegetative (autonomous) neuropathy, age-related baroreflex incompetence syndrome, and potential volume depletion (in case of diarrhoea, vomiting, blood loss, diuretic therapy). Often, episodes of orthostatic hypotonia are combined with postprandial hypotonia, which is caused by an increase in blood filling of GIT organs (usually 2–3 hours after a substantial meal, especially with alcohols). This is a classic mechanism of ischemic cerebral strokes (e.g. the patients comes home from work, eats a lot, lies down to rest, then rises and has both orthostatic and postprandial hypotonia, cerebral hypoperfusion, stroke) [17, 21].

Clinical manifestations of orthostatic hypotonia include episodes of dizziness, weakness, dyspnoea, chest pain, impaired vision associated with quick rising; hypotonia worsens in warm environment and during long-time standing. Syncopal state (also after long-time sitting — for example, during a long car ride, approx. 500–1000 mL of blood is re-distributed to lower limbs, and it contributes to the risk of syncope when rising), falls, fractures are not rare. It has been demonstrated that episodes of orthostatic hypotonia are associated with higher rates of cardiovascular and all cause deaths.

Recommended approaches to reduce the risk of such episodes include discontinuation of antihypertensives, which facilitate orthostatic reactions (such as thiazide diuretics, α-AB, direct vasodilators), consumption of more fluids, compression stockings, avoidance of abrupt verticalisation, avoidance of heat, overeating, hot bath or shower, high stresses (loads). Drug therapy used in type 2 DM patients can include alpha-lipoic acid products; less often — mineralocorticoids; fludrocortisone; desmopressin, a vasopressin analogue; midodrine, a sympathomimetic drug; pyridostigmine, a cholinesterase inhibitor. It has been reported that clonidine can potentially reduce orthostatic reactions, however, this information requires additional confirmation [19, 23].

Orthostatic hypotonia is a sign of cardiovascular autonomic neuropathy (CAN). Other symptoms include sinus tachycardia at rest (monotonous tachycardia); rigid rhythm (no response to physical or emotional stress); painless myocardial ischemia/silent myocardial infarction; sudden cardiac arrest/vegetative denervation. At early stages, CAN can be completely asymptomatic and can be diagnosed only after evaluation of heart rhythm variability with deep breathing. In advanced cases, patients present with tachycardia at rest, when heart rate is as high as 100 bpm, and poor exercise tolerance. Moreover, a majority of CAN cases are not associated with compensatory rise in the heart rate upon verticalisation, despite developing hypotonia (chronotropic failure). Most often CAN symptoms appear in vertical position and include dizziness, weakness, palpitations and collapse [11, 13].

Timely CAN diagnosis is essential, since this type of neuropathy in DM patients is an independent cardiovascular risk factor. CAN in type 2 DM patients is associated with higher mortality rates. CAN can become more severe with fluctuations in glycaemia levels (especially with episodes of hypoglycaemia). It has been demonstrated that reduction in heart rate variability (CAN marker) is a direct independent cardiovascular risk factor in pre-diabetes patients. Glycaemia control is essential for CAN prevention [10, 12].

Management of Patients with AH and Type 2 DM

Antihypertensives

The most commonly used antihypertensives are ACE inhibitors, sartans, CCBs, thiazide-like diuretics, MRA and β-AB. α-AB, renin inhibitors, loop diuretics, drugs for CNS activity (methyldopa or clonidine) and product to directly reduce smooth muscle strain in vessels (e.g. hydralazin), are less common. The final choice of antihypertensives depends on a number of factors, such as comorbidities, GFR and adverse effects [19, 22].

ACE inhibitors and sartans significantly reduce the number of type 2 DM cases in patients with arterial hypertension or congestive heart failure, possibly due to improved insulin secretion and better insulin sensitivity

[25, 26]. They are highly recommended as first-line therapy in patients with AH, DM and IHD; since it has been proven that they reduce cardiovascular risks in diabetic patients [25-29]. They should be added to the therapy as soon as possible in order to prevent blood vessel remodelling [30]. Besides, they should be first-line drugs in patients with AH, DM and severe albuminuria (albumin/creatinine value of > 300 mg/g) and should be considered when albumin/creatinine value is 30–299 mg/g, since they reduce the risk of kidney disease progression [31]. In the HOPE study, ramipril significantly reduced the risk of combined endpoints, all cause deaths and hospitalisations due to heart failure, when used in patients with DM and microalbuminuria [33]. In the ADVANCE RCT, addition of perindopril and indapamide reduced the rate of cardiovascular and all cause deaths and the number of macro- and microvascular complications in patients vs. placebo [32]. The ACHIEVE RCT demonstrated that ACE inhibitors and dihydropyridine CCBs are superior to the therapy with ACE inhibitors and thiazide diuretics as regards reduction of adverse cardiovascular events in patients with and without DM; however, the hydrochlorotiaside dose used in the trial was below the level required for efficient CVD reduction [33, 34].

Other drugs affecting RAT are MRAs, spironolactone and eplerenone. It has been established that the addition of spironolactone to the standard antihypertensive therapy reduces albuminuria levels in patients with DM and DNP [35]. Also, the addition of spironolactone to a minimal dose of lisinopril resulted in better renal protection in DNP patients as compared to the same dose of losartan and ACE inhibitors [36].

CCBs are recommended as a first-line therapy in DM patients, especially in elderly patients with ISAH [37]. Previous studies assumed that CCBs were able to prevent DM by inhibition of β-cell apoptosis and improvement of β-cell function; however, the meta-analysis by Noto et al. did not prove this hypothesis [38, 39].

Therefore, ACE inhibitors, BRAs, CCBs and thiazide-like diuretics are acceptable for initial antihypertensive therapy in DM patients. It is important to take into account adverse effects of antihypertensives, especially those associated with cardiometabolic consequences. Thiazide-like diuretics (e.g. chlortalidone) can result in hyperglycaemia because of their ability to enhance insulin resistance [40, 41]. Besides, a majority of β-ABs are not recommended as a first-line therapy in DM patients due to their adverse cardiometabolic effects: increased triglyceride levels, reduced HDL cholesterol levels, suppression of hypoglycaemia symptoms and reduced insulin sensitivity [42]. Also, it is assumed that they can increase the risk of DM, especially in obese individuals, as compared to alternative drugs [43]. However, not all β-ABs have adverse effect for glucose homeostasis. Carvedilol, nebivolol, labetalol not only block β-adrenoreceptors, but also have additional properties facilitating vasodilatation and causing less adverse effect for metabolism [44]. These effects were studied in the GEMINI RCT in type 2 DM patients with AH. The study compared metabolic and glycaemic effects of metoprolol tartrate and carvedilol therapy. The use of carvedilol did not affect glycaemia control and improved insulin sensitivity. It appears that the lowest probability of DM de novo resulting from antihypertensive therapy is with the use of sartans, ACE inhibitors and, to a lesser extent, CCBs [45].

Lipid-lowering agents

CVRs in patients with AH and type 2 DM are high and even very high in the presence of DNP. In order to reduce CVRs, it is recommended to use lipid-lowering agents in addition to life-style changes. When lipid-lowering agents are used, it is advisable to aim to achieve the target low density lipoprotein cholesterol (LDL-C) levels, which are: 1)< 1.8 mmol/L (in high CVR) or < 1.4 mmol/L (in very high CVR), or at least 50 % reduction vs. baseline. The first-line therapy are high or maximum tolerable doses of sartans. If, despite the use of sartans, the target LDL-C levels are not achieved, it is recommended to add ezetemibe to sartans; if this combination is unable to achieve the target LDL-C values, then PCSK9 inhibitor can be used as an additional measure [46, 47].

Antiplatelet drugs

In type 2 DM patients with AH, if they have DNP and atherosclerotic cardiovascular involvement, a very high risk of cardiovascular risk necessitates the use of acetylsalicylic acid (ASA) 75–100 mg/day as a preventive measure. If not tolerated, clopidogrel can be used as an alternative to ASA. A dual antiplatelet therapy comprising ASA and platelet P2Y12-receptor inhibitors (ticagrelor, clopidogrel) is recommended for patients who underwent scheduled coronary stenting (usually no more than 6 months), as well as for post-acute coronary syndrome individuals (usually no more than 12 months) [11, 27].

Glycaemia control

In type 2 DM patients with chronic IHD, metformin is the leading antihyperglycemic drug; if necessary, other drug classes are added to metformin. After information from a number of RCTs has been received on the

favourable effects for cardiovascular and renal prognosis of the two new classes of antihyperglycemic drugs, glucagon-like peptide-1-receptor agonists (GLP1ra) (AWARD-7 RCT) and iSGLT2 (EMPA-REG, CANVAS, DECLARE, CREDENCE, DAPA-HF RCTs), experts give priority to these classes (usually, in addition to metformin). If GLP1ra and/or iSGLT2 cannot be prescribed in addition to metformin, other antihyperglycemic drug classes can be added (which do not improve prognosis, but are more readily available).

In type 2 DM patients with DNP who have preserved or moderately impaired renal function (stage 1–3 CKD, GFR > 30 mL/min/1.73 m^2), a combination of metformin with GLP1ra and/or iSGLT2 is preferable. If GLP1ra or iSGLT2 cannot be used for economic reasons, then metformin can be supplemented with DPP-4 inhibitors, sulfonylureas, pioglitazone for glycaemic control in patients with DNP and GFR > 30 mL/min/1.73 m^2 [11, 24].

Conclusion

To conclude this literature review, the presented material can be summarised as follows (Fig. 2). AH is a crucial factor of a cardiovascular and renal risk both in general population in among type 2 DM patients. In turn, type 2 DM is a cause of a variety of macro- and microvascular complications; it is a separate and independent cardiovascular risk factor. Very often, AH and diabetes are comorbidities; they share common pathogenesis characteristics and mutually aggravate each other.

In the management of type 2 DM patients with AH, it is highly essential to follow the life-style change recommendations, including healthy eating, reduced sodium chloride consumption, graduated exercises, slimming, smoking cessation, reduced alcohol consumption. The most common target BP levels in this category of patients are 120–130/ 70–79 mm Hg, with target HbA1C values of 6.5–7.0 %. Literature data on the features of the course of AH and antihypertensive therapy in AH in combination of type 2 DM are very controversial. A number of specialists emphasise that the pattern of AH in these individuals is close to the pattern in individuals without diabetes, and there are no special features. At the same time, other researchers point out a number of aspects, that distinguish type 2 DM patients with AH from the general AH population, namely: salt sensitivity predisposition (so AH is often volume-dependant), a higher rate of circadian

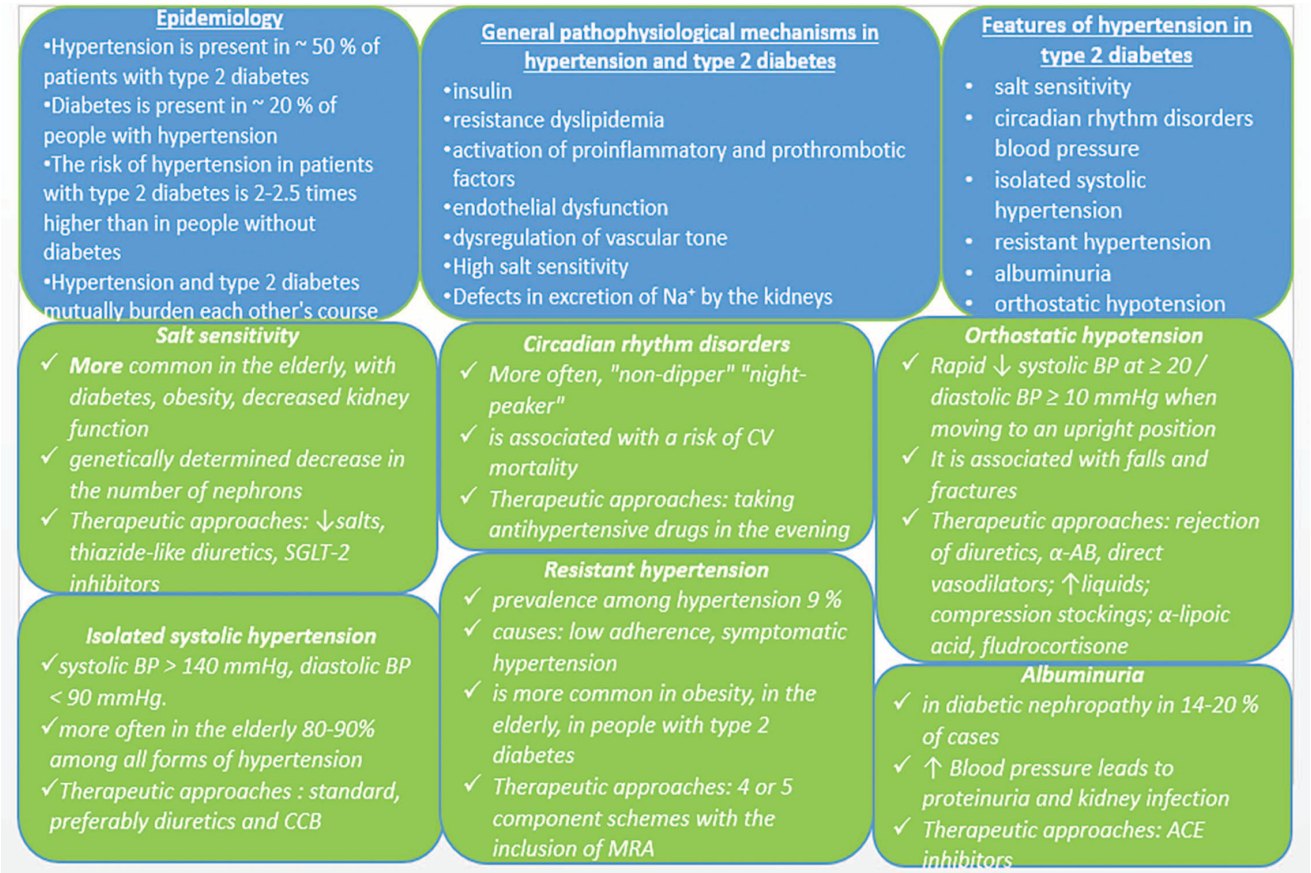

Figure 2. *Arterial hypertension in type 2 diabetes mellitus*

BP rhythm abnormalities (with a higher rate of non-dippers and night-peakers), ISAH, resistant AH, a combination with albuminuria, episodes of orthostatic hypotonia. While the assumption that RATS blockers, including ACE inhibitors and sartans, have a dominant role in the management of AH with type 2 DM, is well-established, possible use of other classes of drugs in these patients, including MRAs, imidazoline receptor agonists and SGLT-2i, requires additional studies [11, 17, 23].

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РЕГИСТР РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКИ ВЫЯВЛЯЕМОСТИ АЛЬБУМИНУРИИ СРЕДИ ПАЦИЕНТОВ С РАНЕЕ НЕДИАГНОСТИРОВАННОЙ ХБП — АУРА

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Real Clinical Practice Register of Albuminuria Detection in Patients with Previously Undiagnosed Chronic Kidney Disease

Резюме

Цель: сбор данных о фенотипе пациента с наибольшим риском развития альбуминурии и оценка её распространенность в выявленных фенотипах, а также получение данных о характеристиках, назначаемой терапии, сопутствующей патологии пациентов с и без выявленной альбуминурии. **Материалы и методы.** Информация о распространенности альбуминурии в популяции собирается одномоментно в рамках регистра реальной клинической практики. Все пациенты, обращающиеся за медицинской помощью, оценены на предмет наличия альбуминурии и её степени, все данные собраны в обезличенном виде и внесены в электронную регистрационную карту. Критерии включения: 1) мужчины и женщины в возрасте от 40 лет и старше на момент регистрации данных; 2) возможность выполнить тест на альбуминурию с использованием тест-полосок и/или анализа на микроальбуминурию или соотношение альбумин/креатинин в разовой порции мочи. Критерии невключения: 1) нежелание пациента участвовать в регистре; 2) наличие диагноза ХБП выставленного до момента скрининга в регистр; 3) наличие диагнозов сахарный диабет 1 и 2 типа, выставленных до момента скрининга в регистр; 4) беременность; 5) бег на длинные дистанции или очень тяжелая физическая нагрузка за последние 24 часа. **Результаты.** На момент предоставления данного материала проходит активная фаза набора пациентов в регистр с учётом заявленной мощности. С учетом предполагаемой скорости набора участников регистра в 45–50 центрах ожидается, что в регистр будут включены данные по 12.000–15.000 пациентам. Если удастся набрать менее чем 12.000 субъектов и расчетная скорость набора в регистр будет недостаточной, может быть увеличено количество исследовательских центров или расширен период скрининга. **Заключение.** Несмотря на установленную прогностическую значимость данных об АУ, в широкой практике данный анализ назначается лицам из групп риска по развитию ХБП или пациентам с уже установленной нефрологической патологией. Проведение локального регистра, объединяющего различные популяции пациентов, в первую очередь, включающего пациентов не только из установленных групп риска по развитию ХБП, а также с использованием тест полосок на определение АУ представляет научный и практический интерес и может быть использовано при написании национальных рекомендаций, учебно-методических пособий, использоваться в клинической практике.

Ключевые слова: *альбуминурия, хроническая болезнь почек, регистр*

Конфликт интересов

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

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Abstract

Aim. To collect data on the patient phenotype at the highest risk of developing albuminuria, to assess the prevalence of albuminuria in the identified phenotypes, and to collect data on the characteristics, prescribed therapy, and comorbidities of patients with and without identified albuminuria. **Materials and methods.** Data on presence or absence of albuminuria are collected in this register of real clinical practice instantaneously. All patients seeking medical attention are screened for the presence and extent of albuminuria. All data are collected in anonymized form and entered into an electronic case report form. Inclusion criteria: 1) men and women aged 40 years and older at the time of data collection; 2) the possibility to perform an albuminuria test using dipsticks and/or a test for microalbuminuria or urine albumin/creatinine ratio in a spot urine sample. Exclusion criteria: 1) the patient's reluctance to participate in the registry; 2) diagnosis of CKD made before screening for the registry; 3) diagnosis of diabetes mellitus type 1 or 2 made before screening for the registry; 4) pregnancy; 5) long distance running or very heavy physical activity in the last 24 hours. **Results.** At the time of submission of this material, the active phase of patient recruitment for the registry with the specified power has been ongoing. Based on the expected recruitment rate at 45–50 sites, the registry is expected to include data from 12,000–15,000 patients. If fewer than 12,000 patients are recruited and the estimated recruitment rate for the registry is insufficient, the number of study sites or the screening period may be extended. **Conclusion.** Despite the established prognostic significance of the data on AU, the test is prescribed in routine practice to individuals at risk of developing CKD or to patients with an established nephrological disorder. A local registry that combines diverse patient populations, namely patients not only from established CKD risk groups but also patients with a dipstick test for AU, is of scientific and practical interest and can be used in the development of national clinical guidelines and educational materials and used in clinical practice.

Key words: *albuminuria, chronic kidney disease, registry*

Conflict of interests
The authors declare no conflict of interests

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BP — blood pressure, AH — arterial hypertension, AU — albuminuria, ARA — angiotensin 2 receptor antagonists, ARNI — angiotensin receptor and neprilysin inhibitors, ACE inhibitors — angiotensin converting enzyme inhibitors, IHD — ischemic heart disease, BMI — body mass index, CRF — case record form, HDL — high-density lipoproteins, LDL — low-density lipoproteins, KSD — kidney stone disease, IFG — impaired fasting glycaemia, IGT — impaired glucose tolerance, non-HDL — non-high-density lipoproteins, IEC — Independent Ethics Committee, OAC — oral anticoagulants, TC — total cholesterol, POAC — peroral anticoagulants, DM — diabetes mellitus, e-GFR — estimated glomerular filtration rate, GFR — glomerular filtration rate, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, CVD — cardiovascular diseases, TG — triglycerides, RF — risk factors, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, CCF — chronic cardiac failure, RR — respiratory rate, HR — heart rate, EC — ethics committee, EDG — electronic data gathering, IRB — Institutional Review Board, CKD-EPI 2021 — Chronic Kidney Disease Epidemiology Collaboration 2021, iSGLT 2 — sodium glucose linked transporter inhibitors, KDIGO — Kidney Disease: Improving Global Outcomes

Introduction

Albuminuria (AU) is the presence of albumin in urine, where the normal urine concentration in the morning can be < 30 mg/mL (< 3 mg/mmol) [1]. AU is a sign of impaired kidney function and is associated with a higher risk of progressive loss of kidney functions over time. At early stages, a majority of kidney disorders are symptomatic, while the therapy of terminal CKD, including dialysis and kidney transplant, is expensive. Therefore, it is crucial to search for markers of early CKD. In 2012, the KDIGO (Kidney Disease: Improving Global Outcomes) published recommendations for CKD diagnosis and management, with a new classification based on a combined measurement of the rate of glomerular filtration rate reduction and albuminuria/proteinuria severity [1].

In addition to its role in early diagnosis and risk assessment for CKD patients, AU is an important prognostic marker of cardiovascular diseases (CVD) and diabetes mellitus (DM). Schmieder et al. assessed the role of increased AU levels in spot urine over time in 23,480 patients with CVDs and DM. It has been shown that at least 2-fold increase in AU over 2 years vs. baseline is greatly associated with CVD mortality, combined cardiovascular outcomes (cardiovascular death, myocardial infarction, stroke and hospitalisation for cardiac failure) and renal outcomes, including dialysis and doubled serum creatinine levels [2, 3].

The National CKD Clinical Recommendations are based also on mandatory AU screening in patients with a high risk of CKD, and four albuminuria stages have been identified depending on albumin concentrations in 24-hour urine or albumin-creatinine ratio in spot urine [4]. It is worth mentioning that if a patient has CKD and CVD, it forms a vicious circle, where one condition causes progression of the other. In particular, it has been proven that AU contributes to endothelial dysfunction development and aggravation in DM patients. In AH, DM, CCF and obesity, albuminuria monitoring is essential for early diagnosis of CKD, and it is advisable to use assessment of urine albumin-creatinine ratio.

Besides, changes in AU levels with the use of renoprotective therapy are also a marker of therapy efficacy, making AU an CKD monitoring marker.

Despite the identified prognostic value of AU data, in real life this test is indicated for individuals in CKD risk groups or for patients with a diagnosed renal pathology. However, it is still necessary to obtain data on albuminuria prevalence in patients with and without known CKD risk factors and to identify qualitative characteristics in the identified population.

The common goal of this register is to gather information on a patient phenotype with the highest risk of albuminuria and to assess its prevalence in identified phenotypes, as well as to obtain information on characteristics, therapy, comorbidity in patients with and without diagnosed albuminuria.

Register Design, Endpoints, Organisation and Data Gathering

The AURA Register is a multicenter, non-interventional register of actual clinical practice. No patient follow-up is planned (cross-sectional design). Patient

enrolment start date is March 6, 2023; enrolment is expected to end on April 1, 2024.

All study sites use standardised case record forms (CRF). Information is gathered by GPs strictly in accordance with inclusion and non-inclusion criteria. Each CRF is reviewed by organiser's Monitors. According to good clinical practice, all data entered in the Register by Investigators are anonymised. Each patient is assigned a unique ID number when information is entered in CRF.

The main purpose of the Register is to obtain descriptive data on main phenotypes of patients with albuminuria and to study therapies in these patients with due account of comorbidities.

The Register territory is 45–50 sites in 7 federal districts of the Russian Federation (Privolzhsky, Northwest, North Caucasian, Siberian, Ural, Central, Southern). The expected Register capacity is 12,000 patients.

An ethics review of this Register was performed 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 Russia on February 22, 2022 (Excerpt No. 226 from the LEC meeting minutes).

Registration number of the study at ClinicalTrials.gov is NCT-05690009.

Patient Population

The Register includes both male and female patients over 40 years of age who were previously diagnosed with such diseases as CKD, type 1 DM, type 2 DM. For a detailed description of inclusion and non-inclusion criteria, please refer to Table 1.

Other characteristics are detailed in Section 7.1.3. of the Register Protocol.

Table 1. *Criteria for inclusion and non-inclusion in the registry AURA*

Inclusion criteria
• Men and women 40 and older at the time of data registration
• Ability to perform an albuminuria test using test strips and/or albumin/creatinine ratio analysis in a single urine sample
Inclusion criteria
• Patient's unwillingness to participate in the registry
• Presence of a diagnosis of CKD made prior to screening in the registry
• Type 1 and type 2 DM diagnosed prior to screening in the registry
• Pregnancy
• Physical activity in the last 24 hours

Statistical Analysis

Statistical processing comprises the following stages:

1) Exploratory analysis: identification of outliers; a check of normality of quantitative variable distribution; preliminary identification of correlations using correspondence analysis, correlation matrix and graphic analysis.
2) Data cleaning and transformation: replacement of missing values, removal of outliers, data normalisation and conversion if necessary (creation of new variables, numeric variable grouping, categorical variable re-grouping).
3) If necessary, sample reduction (exclusion of observations) to secure representativity.
4) If necessary, formation of additional hypotheses based on the exploratory analysis, e.g. differences between patients with varying degrees of albuminuria, correlations between individual laboratory/instrumental results, etc.
5) Preparation of descriptive statistics: qualitative variable frequencies, measures for alignment and dispersion of quantitative variables (2 groups: patients with and without albuminuria):
   - Albuminuria incidence within the Register
   - Sex and age characteristics of patients
   - Results of laboratory and instrumental diagnostics
   - Comorbidities and concomitant therapy
6) Analysis of correlation between individual variables and the presence of albuminuria and/OR albuminuria severity (chi-square criterion, analysis of variance/Kruskall-Wallis test)
7) Multiple factor analysis of the risk of AU: logit regression and/or decision trees.

   Model robustness will be achieved due to a) preselection of predictors at step 6, and b) repeated iterative evolution of the model using random patient subsamples.
8) If necessary, testing of additional hypotheses generated at step 4. Data will be processed using IBM SPSS Statistics 25 package.

Discussion

Despite the identified prognostic value of AU data, in real life this test is indicated for individuals in CKD risk groups or for patients with a diagnosed renal pathology. In a meta-analysis by Coresh et al. of 693,816 patients, of which 80 % had confirmed DM, changes in the ratio of albumin/creatinine or protein/creatinine in spot urine

over 2 years were evaluated [5]. A meta-analysis by Matsushita et al., where AU was used as a prognostic factor of a cardiovascular risk, included 637,315 patients with confirmed cardiovascular pathologies [6]. Besides, such AU assessments use measurement of albumin/creatinine ratio in spot urine or daily urine albumin excretion [7]. Sumida et al. studied patients over 18 years of age, of which 56 % had DM and 72 % had arterial hypertension. 919,383 patients were screened using both standard laboratory methods (albumin/creatinine ratio in spot urine) and AU test strips, which complies with KDIGO recommendations [1, 8].

Within the scope of a prospective non-interventional observational study "Early diagnosis of chronic kidney diseases in primary healthcare facilities" in real clinical practice, which was conducted in 12 regions of the Russian Federation, 1,124 patients out of 13,968 patients who visited primary healthcare facilities had risk factors of CKD and were referred to an initial consultation by a nephrologist [9].

Also, among Russian studies of CKD, of interest is CHRONOGRAPH (a non-interventional observational open-label multicenter program to gather information on CKD markers in patients with arterial hypertension with or without type 2 DM in the Russian Federation) [10]. In this program, 1,363 patients with AH and/or type 2 DM had their GFR calculated and AU measured using the albumin-creatinine ratio in morning urine.

Conclusion

This data suggest that a local register of various patient populations, including first of all patients not only from identified groups of CKD risk, but also using AU test strips, has scientific and practical potential and can be used in the preparation of national recommendations, study guides and also in clinical practice.

The authors realise that occasionally identified albuminuria is not a sign of CKD, but just a laboratory phenomenon, which in some cases is physiological (functional). Therefore, CKD verification requires a repeated measurement 3 months later, and it was proposed to the patients outside this protocol. Meanwhile, even a single event of albuminuria should be included in risk factors of renal and cardiovascular pathologies; this was demonstrated earlier in a number of studies and, therefore, is a useful screening tool for preselection of patients for a more thorough, also repeated examination.

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ИНФАРКТ СЕЛЕЗЕНКИ И ИНФАРКТ МИОКАРДА У БОЛЬНОГО COVID-19 НА АНТИКОАГУЛЯНТНОЙ ТЕРАПИИ С НОРМАЛЬНЫМ УРОВНЕМ D-ДИМЕРА

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Splenic Infarction and Myocardial Infarction in A Patient with COVID-19 on Anticoagulant Therapy with Normal D-Dimer Levels

Резюме

Многие исследования показали, что COVID-19 может прогрессировать с коагулопатией и мультисистемными тромботическими патологиями. В данной статье представлен случай пациента, у которого через 9 дней после лабораторно подтвержденной коронавирусной пневмонии на фоне антикоагулянтной терапии был, при повторной госпитализации, диагностирован инфаркт селезенки в сочетании с последующим острым инфарктом миокарда. Предупреждение тромбоза профилактическими дозами низкомолекулярного гепарина у госпитализированных пациентов с COVID-19 может оказаться недостаточным для предотвращения развития коагулопатии. Следует заподозрить у COVID-19-положительного пациента с болью в животе абдоминально-висцеральную тромбоэмболию, несмотря на антикоагулянтную терапию и нормальный уровень D-димера.

Ключевые слова: *инфаркт селезенки, COVID-19, острый инфаркт миокарда, коагулопатия, тромбоз*

Конфликт интересов

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

Источники финансирования

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Abstract

Many studies have shown that COVID-19 can progress with coagulopathy and multisystem thrombotic pathologies. This article presents the case of a patient who, 9 days after laboratory-confirmed coronavirus pneumonia against the background of anticoagulant therapy, was diagnosed with splenic infarction in combination with acute myocardial infarction during subsequent hospitalization. Prevention of thrombosis with prophylactic doses of low molecular weight heparin in hospitalized patients with COVID-19 may not be sufficient to prevent the development of coagulopathy.

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Abdominal visceral thromboembolism should be suspected in a COVID-19 positive patient with abdominal pain despite anticoagulant therapy and normal D-dimer levels.

Key words: *splenic infarction, COVID-19, acute myocardial infarction, coagulopathy, thrombosis*

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SI — splenic infarction, MI — myocardial infarction, CT — computer tomography, LMH — low molecular heparin, VTE — venous thromboembolism

Introduction

COVID-19 is a viral multisystem disease caused by SARS-CoV-2 respiratory virus [1]. During COVID-19, susceptibility to arterial and venous thromboembolism caused by impaired coagulation was observed [2]. Thromboembolic complications are multisystem and most often involve lungs, heart, brain, kidney, bowels, and spleen [2]. Increased D-dimer and low antithrombin levels are one of the factors associated with a higher risk of thromboembolism; however, the available data failed to clearly explain the cause of such clotting disorder.

This article describes splenic infarction (SI) with acute myocardial infarction (MI) after COVID-19 infection; the aim is to emphasise the need for diagnostic vigilance concerning severe thromboembolic complications in COVID-19 patients, irrespective of anticoagulant therapy and low D-dimer levels.

Case Study

On March 17, 2023, a 45-year-old male was admitted to the admissions room of Simferopol State Clinical Hospital No. 7 with cough and sore throat. The medical history was unremarkable. The patient did not have any drug allergies; he did not smoke, did not consume alcohol or medicinal products. Body mass index (BMI): 22.7. Upon admission, blood oxygenation: 88 %, heart rate (HR): 104 bpm, blood pressure (BP): 105/75 mm Hg, body temperature: 38.5 °C. Chest CT demonstrated typical signs of COVID-19 pneumonia. Nasopharynx PCR swabs came back positive for SARS-CoV-2 infection. D-dimer level was 460 ng/mL DDU (normal value: < 243). Prescribed therapy: antivirals (favipiravir), dexamethasone 6 mg, anticoagulating agent (enoxaparin 40 mg) and oxygen support, which was gradually reduced along with improved oxygenation.

Upon discharge on March 23, 2023, the patient was recommended to take low molecular heparin (LMH); blood oxygenation was 94 %, HR — 78 bpm, HR — 120/70 mm Hg, body temperature — 36.5 °C. Two days letter, the patient sought medical assistance in the admissions ward with pain in the left hypochondrium and left side of the body, which persisted for a day. Physical examination was unremarkable, except for mild tenderness in the left hypochondrium with no signs of peritonitis. Complete blood count revealed leukocytosis: 17.2×10^9/L. D-dimer of 150 ng/mL (< 243) and troponin of 0.001 (0–0.29) were within the normal range. Abdominal CT showed an unenhanced hypodense area of approx. 57 × 48 mm, extending from splenic capsule to splenic hilum in the middle of spleen (Fig. 1).

Chest CT showed prevailing subpleural ground-glass opacity and interseptal thickening in both lungs. The pattern corresponded to a typical chest CT pattern of COVID-19 obtained 9 days before (Fig. 2).

The patient stopped taking LMH. Intravenous hydration and non-opioid analgesics were initiated. Anticoagulant (enoxaparin) dose was increased to 80 mg. On day one of his readmission, the patient complained of chest pain. ECG demonstrated elevated ST segment in limb leads (II, III, aVF), evidencing acute lower MI. The patient was referred to cardiologists for consultation. EchoCG did not show any clots in the heart. Cardiovascular surgeons performed urgent coronary angiography. The patient was under observation in ICU after successful stenting of the subclavian artery. Once his haemodynamics were stable, the patient was transferred to a general surgical ward. During hospitalisation, abdominal pain reduced with the use of low-dose painkillers. Oral anticoagulants were gradually increased. The patient was discharged and recommended taking acetylsalicylic acid 100 mg and ticagrelor 90 mg twice daily. Genetic hypercoagulation testing, including lupus anticoagulant

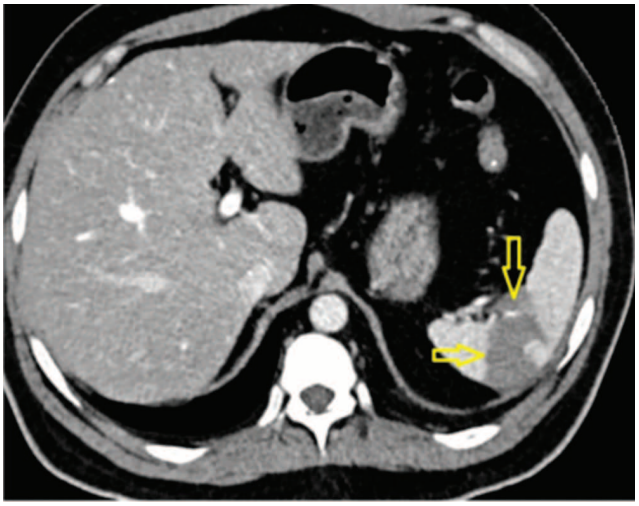

Figure 1. *Abdominal CT. Arrows indicate the hypodense area.*

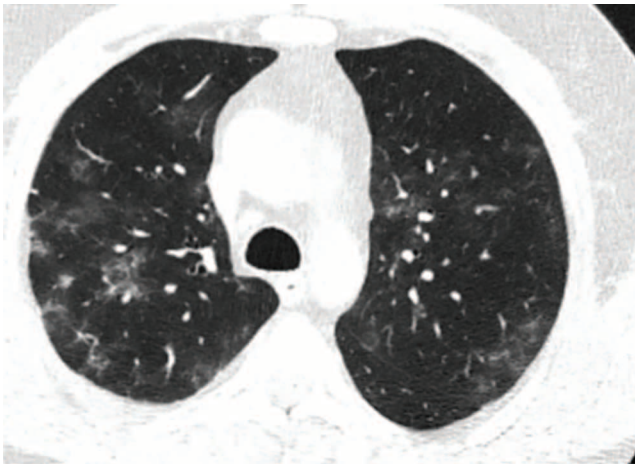

Figure 2. *Chest CT. Ground-glass opacities and interseptal thickening.*

and antiphospholipid syndrome: negative. A follow-up ultrasound examination 3 months later did not show any pathological changes in the spleen, therefore, splenectomy was not required. The infectious disease ward did not deem it necessary to vaccinate the patient agianst meningococcal and haemophilus influenza; also, the X-ray department concluded that repeated chest imaging would not be necessary.

Discussion

Most often thromboembolic complications involve lungs and are rarer in the heart, brain, kidney, GIT, and spleen of COVID-19 patients [1]. Such thromboembolic complications can be observed in COVID-19 patients, as see in this case study. SI is a rare condition, the aetiology of which involves a number of predisposing factors, such as obesity, malignancies, cardioembolic complications, vasculitis, autoimmune disorders, atrial fibrillation, a history of endocarditis, RBC abnormalities, and hypercoagulation [3]. It is rare in COVID-19 patients. In literature, 92 % of SI cases seen in COVID-19 patients are diagnosed in males, while the mean age is 60 years [3].

Thromboembolic events are usually observed two weeks after COVID-19 diagnosis. Arterial hypertension is reported as the most common comorbidity in such patients. However, SI is diagnosed in patients without any comorbidities, as seen in this case study. A majority of patients with this condition complain of pain in their left hypochondrium or left side of the body. Symptoms are versatile: from asymptomatic condition to acute abdomen or hematogenic shock [4]. Usually, final diagnosis uses CT imaging.

Such patients can also have elevated D-dimer levels; however, in this case study, the patient had normal examination results [5]. D-dimer is a degradation product of fibrin in a number of thrombotic complications; it was reported that elevated D-dimer levels in patients with COVID-19 pneumonia are associated with a higher risk of venous thromboembolism (VTE), disease severity and mortality [6]. High D-dimer levels have low specificity in VTE, since their levels can be elevated in a number of conditions (pregnancy, sepsis, malignancies, etc.). Despite low specificity, a normal D-dimer level may not be indicative of the absence of a VTE event [7]. Studies of aetiopathogenesis of thromboembolic complications in patients with a positive COVID-19 test explain resulting endothelial damage, blood-clotting disorder caused by severe viral sepsis, virus-induced antiphospholipid syndrome and systemic inflammatory response syndrome [2]. Although elevated D-dimer and low antithrombin levels are among factors associated with complications, the cause of this clotting disorder cannot be explained clearly.

Traditional medical follow-up with the use of anticoagulation therapy is usually enough for the management of patients with SI. However, due to splenic bleeding, aneurysm, spontaneous rupture and splenic abscess, such patients can require surgery. Also, a risk of infection can be high in post-splenectomy patients. Patients with positive COVID-19 test are at a higher risk of pulmonary complications and mortality as a result of early surgeries [8]. Thus, patients should be observed as close as possible.

A risk of thromboembolism is higher in patients with chronic conditions, obesity, high D-dimer levels and positive COVID-19 test [7]. One peculiarity distinguishing this case study among other patients with SI is that the patient did not have any predisposing factors, which could aggravate thromboembolism and elevate D-dimer

levels, while after SI diagnosis the patient was taking anticoagulant therapy. Despite higher LMH doses, on day one of readmission the patient developed MI, which was successfully managed with urgent coronary angiography. Thus, preventive anticoagulation therapy is essential for prevention of arterial and venous embolism after discharge, even in the absence of high risk factors, obesity, higher D-dimer levels and limited mobility of patients with COVID-19 pneumonia [9].

Conclusion

After discharge, all COVID-19 patients are recommended taking preventive doses of anticoagulants; however, thrombosis prevention with LMH can be insufficient in prevention of blood-clotting disorders in patients hospitalised with COVID-19-associated pneumonia. Prospective studies in patients who do not have any risk factors of this condition will help to develop an optimal post-discharge prevention and management.

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ТРУДНОСТИ ДИАГНОСТИКИ АБСЦЕССА ПОДВЗДОШНО-ПОЯСНИЧНОЙ МЫШЦЫ У ПАЦИЕНТКИ С ХРОНИЧЕСКИМ БОЛЕВЫМ СИНДРОМОМ

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Difficulties in the Diagnosis of Iliopsoas Muscle Abscess in a Patient with Chronic Pain Syndrome

Резюме

Абсцесс подвздошно-поясничной мышцы является редкой хирургической патологией, что в совокупности с особенностями ее расположения обусловливает трудности диагностики данной патологии. При этом своевременно поставленный диагноз будет определять благоприятный прогноз для пациента. В статье описан клинический случай пожилой пациентки с лихорадкой и интоксикационным синдромом на фоне хронического болевого синдрома. Длительное течение болевого синдрома осложняло диагностический поиск и затрудняло постановку диагноза. Подвздошно-поясничный абсцесс следует включить в дифференциальный ряд состояний у пациентов, имеющих лихорадку, боль в ногах, анталгическую походку с ограничением движений бедра, а также положительный псоас-симптом. Информирование врачей о клинических проявлениях абсцесса подвздошно-поясничной мышцы важно для своевременной диагностики данного угрожающего жизни состояния.

Ключевые слова: *абсцесс подвздошно-поясничной мышцы, хронический болевой синдром, трудный диагноз, редкий случай*

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

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Abstract

Iliopsoas muscle abscess is a rare surgical pathology that, in the beginning with the main location of the muscles, determines the diagnosis of this disease. A timely diagnosis will determine a favorable prognosis for the patient. The article describes the case of an elderly patient with fever and intoxication syndrome against the background of chronic pain syndrome. The long course of the pain syndrome complicated the diagnostic search and forced diagnosis. The iliopsoas abscess includes a differential range of disorders in patients, detection of fever, pain in the legs, antalgic gait with closure of the thigh muscles, and a positive psoas symptom. Informing doctors about the manifestations of iliopsoas muscle abscess, the importance of diagnosing this life-threatening condition.

Key words: *iliopsoas muscle abscess, chronic pain syndrome, difficult diagnosis, rare case*

Conflict of interests

The authors declare no conflict of interests

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BP — blood pressure, IPA — iliopsoas abscess, VAS — visual analogue scale, NSAID — nonsteroidal anti-inflammatory drugs, PCR — polymerase chain reaction, GFR — glomerular filtration rate, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, RR — respiratory rate, HR — heart rate

Iliopsoas abscess (IPA) is a rare surgical pathology which is characterised by a pyoinflammatory process in the iliopsoas muscle and high mortality (up to 19 %). In Russia, there are a few reports on this condition; it is worth mentioning the data by Davidov M. I. et al. that IPA affects 0.01 % of the total number of surgical patients [1].

IPA can be primary or secondary. Primary sources are suppurative foci in skin and adipose tissue of the lower body, from where an infectious agent spreads via lymph tubes; and isolated suppurative foci in skin and adipose tissue, primarily in the trunk and upper body, which spread to the iliopsoas muscle with blood. The factors predisposing to primary IPA are diabetes mellitus, a history of intravenous use of drugs, HIV infection, renal insufficiency, and compromised immunity [1, 2]. Also, IPA can be a complication of medical procedures on the spine or adjacent tissues (blocks, minimally invasive surgeries). The most common cause of secondary IPA is Crohn's disease; other causes are presented in Table 1 [2].

Low incidence of IPA and the fact that the muscle lies in retroperitoneum close to the nerve plexus and other organs contribute to untimely diagnosis of this pathology. According to various authors, IPA is diagnosed weeks and even months after disease onset, or perioperatively during acute abdomen surgery [3]. Initially, radiculitis, sacroilitis, coxarthrosis, lumbar ischialgia, paranephritis, appendicular lump are suspected. Challenging diagnosis is also due to an unclear clinical pattern because of non-steroidal anti-inflammatory drug administration, since radiculopathy and lumbar ischialgia are the main neurological manifestations. Therefore, the search for specific clinical markers of this condition is a burning issue. Gezer A. et al. recommend paying attention to the classic symptomatic triad of IPA: lower back pain, lameness and continuous fever with daily episodes of high temperature [4]. According to Xu B.Y. et al., the main symptoms are fever, leg pain, antalgic gait with limited hip movements [5]. Stolov S. V. et al. recommend assessing the presence of the psoas symptom: bring the patient's hip to abdomen rotating it to the outside, it will cause abruptly increased pain in the iliac and hip region during active and passive attempts to straighten the leg in the hip; deep palpation of the iliac fossa causes marked tenderness, especially during palpitation when the leg is raised (when the iliopsoas muscle strained) [3].

Table 1. *Causes of development of secondary abscess of the iliopsoas muscle*

Pathology of the gastrointestinal tract	Crohn's disease, diverticulitis, appendicitis, colorectal cancer
Urinary tract diseases	Urinary tract infection, cancer, urolithiasis (external shock wave lithotripsy)
Diseases of the musculoskeletal system	Vertebral osteomyelitis, septic arthritis, sacroilitis
Pathology of blood vessels	Infected abdominal aortic aneurysm, infected femoral vessel
Other	Endocarditis, intrauterine contraceptive device, purulent lymphadenitis, vascular catheterization

Local symptoms always correlate with clinical and laboratory systemic inflammatory response syndrome: fever, other signs of intoxication, leucocytosis with stab shift, toxic neutrophils, increased erythrocyte sedimentation rate (ESR), lower Hb, increased blood C-reactive protein (CRP) levels.

A timely diagnosed pyoinflammatory process and therapy promote better prognosis for the patient.

Case Study

Patient Ch., 65 years old, was transported by the ambulance on September 12, 2022 to the Hospital Therapy Clinic at the Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of the Ministry of Health of the Russian Federation, complaining of high temperature up to 38 degrees, marked weakness, low blood pressure of 70/40 mm Hg, nagging pain in her right hip joint at rest, which worsened when moving, irradiated along the posterior hip and limited active movements. The effect of non-steroidal anti-inflammatory drugs (NSAIDs) lasted for a short period of time.

The history taking revealed that the pain started in 2006 after the fracture of the right shin-bone ectocondyle and the trauma to the right hip as a result of a road accident. After a while, the pain worsened: in 2015, the patient consulted a traumatologist because the pain had worsened; she was diagnosed with stage II–III right-sided posttraumatic coxarthrosis, postmenopausal osteoporosis. Due to this pathology the patient repeatedly underwent analgesic, chondroprotective therapy; also, the patient was repeatedly hospitalised to the Trauma Department for a course of analgesic therapy, including paravertebral blocks. By September 2022, the chronic pain syndrome has reached its peak: the pain was bothering the patient at rest and worsened even with a tiny movement; NSAIDs were ineffective; the patient's quality of life worsened, and the patient was unable to move and care for herself on her own. Since the therapy was ineffective, the patient contacted the pain management ward at the Tomsk Regional Oncology Dispensary, where she was prescribed tramadol therapy for the first time. Also, according to the medical records, on September 3, 2022 the patient had right hip block with an unknown medicinal product. After the block, the patient noticed that the pain had become less intense. However, on September 9, 2022 the patient had a fever of 38°C, she had cough and weakness; the patient refused to eat, and the on-duty general practitioner was called for. The on-duty general practitioner had a coronavirus express test performed, and the test for SARS-COV-2 RNA dd September 9, 2022 was negative. At a repeated home visit by the general practitioner on September 11, 2022, the fever and complaints persisted: the patient was recommended to continue the antiviral, symptomatic therapy and pain management. Despite the therapy, the patient's condition deteriorated, and on September 12, 2022, following the daily blood pressure measurement, the family noted persistent hypotension: blood pressure (BP) of 70/40 mm Hg, and called for an ambulance. The patient was transported to the on-duty medical hospital.

Upon admission, the patient's condition was moderately severe. The patient's consciousness was clear. The skin was clear, of physiological colour. Hip movements are limited; the extent of active and passive movements is restricted because of pain. The patient lies on her back in a defence attitude (frog position). The right lower limb is rotated to the outside; the pain is 9 points on the visual analogue scale (VAS). No swelling is present. The chest is cylinder-shaped; vocal fremitus is symmetric on both sides; percussion sound is pneumonic and similar above symmetric lung sections. Breathing: harsh, no wheezing. Respiratory rate (RR) is 18/minute. Oxygen saturation is 97 %. Cardiac sounds are clear, rhythmic. Heart rate (HR) is 100 bpm. BP: 108/70 mm Hg. Abdomen is soft and nontender. Liver is within the costal margin; its edge is even, elastic, painless. Kidney punch is negative on both sides; kidneys cannot be palpated.

The following laboratory and instrumental examinations were conducted upon admission:

Complete blood count dd September 12, 2022: WBC: 11.9×10^9/L, RBC: 3.8×10^{12}/L, Hb: 113 g/L, Ht: 33 %, platelets: 173×10^9/L.

Blood biochemistry of September 12, 2022: creatinine: 226 μmol/L, urea: 14.0 mmol/L, glucose: 5.5 mmol/L, total bilirubin: 32 μmol/L, direct bilirubin: 22 μmol/L, ALT: 23 U/L, AST: 54 U/L, troponin quality assay: neg.

In the admission ward, the patient was examined by a surgeon, who did not find any signs of acute surgical pathology. Taking into account an episode of hypotension, long-lasting therapy with non-steroidal anti-inflammatory drugs, in order to rule out GI bleeding, the patient underwent fibrogastroduodenoscopy, and no signs of upper gastrointestinal bleeding were found.

Lung X-ray demonstrated some infiltrate in the lower lobe of the left lung.

The top priority was the intoxication syndrome, which was considered to be attributable to pneumonia; also, the following syndromes were identified: pulmonary tissue infiltration syndrome, systemic inflammatory response syndrome, chronic pain syndrome, acute kidney injury

syndrome, which manifested as a significant rise in creatinine and urea levels, probably of mixed origin: toxic (due to an infection and NSAIDs) and prerenal (due to hypotension).

The patient was admitted to the Medical Department with the following preliminary diagnosis:

Primary diagnosis: Mild community-acquired left-sided lower lobe pneumonia, unspecified. Respiratory distress: 0.

Complication: mixed acute kidney injury dd September 12, 2022, nonoliguric variant.

The staff in the admissions department treated the chronic pain syndrome as a sign of bilateral coxarthrosis; therefore, comorbidities included bilateral coxarthrosis (stage II on the left and stage III–IV on the right), functional class IV, chronic pain syndrome, VAS 9 points.

Initial antibacterial therapy included third-generation cephalosporins. Since the patient had persistent pain syndrome, she was prescribed a calculated dose of tramadol (taking into account glomerular filtration rate (GFR)). Detoxication therapy was designed to correct hypotension and acute renal injury. Additional examination included follow-up laboratory tests including CRP levels; lung X-ray for pneumonia assessment. Since multi-organ failure (hypotension + acute renal injury) was suspected, a pneumonia-associated septic process was discussed as well; therefore, sterility blood test, urine culture, procalcitonin quantification were scheduled. A urinary catheter was inserted to control diuresis.

The therapy made it possible to correct hypotention, to normalise nitrogenous waste levels; however, the fever of 38°C, weakness and marked hip pain syndrome persisted; pain management correction was required — morphine injections were initiated. Follow-up tests dd September 19, 2022 showed negative changes — high leukocytosis in complete blood count (WBC: 14.36×10^9/L, RBC: 3.44×1012/L, ESR: 43 mm/h, Hb dropped to 98 g/L, platelets: 187×10^9/L), higher CRP levels and high procalcitonin levels in blood biochemistry (blood biochemistry dd September 19, 2022: creatinine: 63.3 μmol/L, urea: 10.8 mmol/L, glucose: 4.7 mmol/L, K: 5.1 mmol/L, Na: 135 mmol/L, Cl: 100 mmol/L, CRP: 419.0 mg/L, procalcitonin: 5.38 pg/mL). Since the patient had systemic inflammatory response syndrome (fever above 38°C, leukocytosis 14.36×10^9/L), high procalcitonin levels and multi-organ failure (hypotension upon admission and acute kidney injury), a septic process was suspected. Blood culture for sterility was performed. The patient underwent another lung X-ray, which did not show any signs of infiltration. Antibacterial therapy was replaced with penicillins plus betalactamase inhibitors.

In order to further search for the primary source of infection, additional examination was scheduled. Taking into account a marked pain syndrome, the area of interest was the hip joints, which were examined using CT.

Hip CT results dd September 19, 2022: swelling and thickening of the right iliopsoas muscle with swollen adjacent subcutaneous tissue, with reduced muscle density and small subcapsular gas bubbles (Fig. 1).

There are no areas of bone destruction. The articular cavity of the right hip joint is significantly narrowed; the femoral head is compressed; there are areas of cystic reconstruction and deep usuras with marginal spurs. The acetabular roof is dilated because of spurs, with numerous areas of cystic reconstruction and deep usuras. There are bone bridges between the acetabular roof and femoral head (Fig. 2).

The left hip joint is moderately narrowed; the head is not deformed; the acetabular roof is not dilated. The bone cortex integrity is not compromised, and the bone volume is normal. Femoral bones are not deformed; collum-diaphyseal angles are normal. There are marginal spurs on both sides of the contours of greater and lesser trochanters, ischial tuberosity. Pubic articulation surfaces demonstrate signs of moderate subchondral sclerosis, with even, clear contours, with minimal marginal spurs. Opinion: Signs of IPA on the right; signs of osteoarthrosis in the right hip joint, stage III–IV; signs of osteoarthrosis in the left hip joint, stage I. Signs of enthesopathy.

In order to decide on the further management, the patient was consulted by a surgeon and transferred to the Septic Surgery Unit, where the abscess could be drained.

On September 20, 2022, in the Septic Surgery Unit the patient underwent IPA opening using Pirogov's method; 120 mL of serous turbid discharge was drained, and a 15×10 cm cavity formed; the abscess cavity was sanitised and drained; discharge was sampled for culture.

Results of blood culture for sterility (September 21, 2022): growth of Staphylococcus aureus, sensitive to gentamycine 10, clindamycin, linezolid, norfloxacin, cefoxitin, erythromycin, and resistant to penicillin.

The final diagnosis for the patient was:

Primary: Iliopsoas abscess to the right.

Complications: Sepsis (blood culture dd September 21, 2022. St. aureus). Acute mixed origin kidney injury (prerenal + toxic), nonoliguric variant. Left-side lower lobe pneumonia. Respiratory distress: 0.

After surgery, the patient noted pain the in the right iliac region, with persistent fever up to 38.2° C. A follow-up examination revealed negative changes: CRP

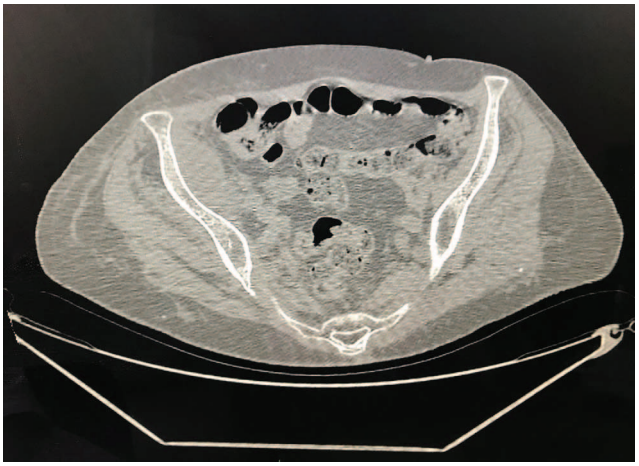

Figure 1. *Computed tomography of the hip joints: swelling and thickening of the iliopsoas muscle on the right with swelling of the adjacent tissue is determined, muscle density is reduced, small gas bubbles are detected subcapsularly*

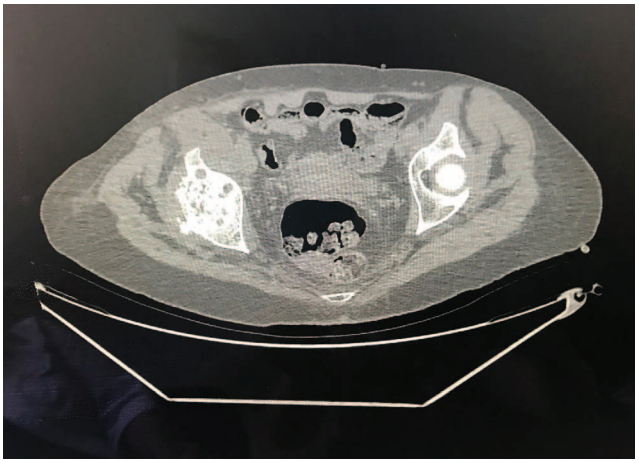

Figure 2. *Computed tomography of the hip joints: the articular space of the right hip joint is sharply narrowed, the head of the femur is flattened, with the presence of areas of cystic restructuring and deep usurs, with marginal osteophytes, the roof of the acetabulum is expanded due to osteophytes, with many areas of cystic restructuring and deep usurs , ankylosis formation*

increase from 419 mg/L to 563 mg/L, hypoalbuminemia (albumin: 22 g/L); all other parameters, including leukocytosis, remain the same (WBC: 14.54×10^9/L, ESR: 52 mm/h).

The post-surgery area was examined using ultrasound of abdomen and right pelvic region, which showed an abscess in the right pelvic area.

On September 22, 2022, the pelvic abscess was drained (100 mL of pus); the wound was dilated. Further revision showed that the abscess cavity extends along the iliac wing and connects to the previously drained cavity (Pirogov's access) on the right. A discharge sample was taken for culture. No microbial growth was recorded.

Despite the surgery and system antibacterials, the patient still had persistent fever up to 38.1°C and pain in the surgery site. Complete blood count demonstrated leukocytosis, with tendency to lymphocyte depletion. In order to rule out coronavirus infection, COVID-19 RNA PCR was performed on September 22, 2022, and the test came positive. According to the routing, since the patient had COVID-19, she was transferred to the respiratory hospital at the Regional State Budgetary Healthcare Institution Primary Healthcare Unit No. 2, Purulent Surgery Department, for further treatment with the following referral diagnosis:

Primary diagnosis: Right iliopsoas abscess, opened and drained on September 20, 2022. Right inguinal abscess, opened and drained on September 22, 2022.

Mild COVID infection (confirmed with PCR on September 22, 2022).

Complications: Sepsis (blood culture dd September 21, 2022. St. aureus). Mixed acute origin kidney injury (prerenal + toxic) dd September 12, 2022, nonoliguric variant. Treated on September 12, 2022. Left-side lower lobe pneumonia. Respiratory distress: 0.

Comorbidity: Stage II hypertensive disease, uncontrolled arterial hypertension. Chronic kidney disease C2 (GFR 71 mL/min/1.73 m^2 for creatinine level dd September 21, 2022). Mild mixed origin anaemia. Bilateral coxarthrosis (stage II on the left and stage III–IV on the right), functional class IV, chronic pain syndrome, VAS 9 points.

Abscess treatment in the respiratory hospital at the Regional State Budgetary Healthcare Institution Primary Healthcare Unit No. 2: daily dressings and antibacterial therapy. Following two negative PCR test results (dd October 10, 2022 and October 11, 2022), on October 12, 2022, the patient was transferred to the Purulent Surgery Department, at City Clinical Hospital No. 3 for further treatment of her primary disease. During hospitalisation, the wounds were treated and healed up.

An ultrasound examination of the lower limb veins which was conducted during hospitalisation revealed some signs of occlusive thrombosis of medial veins of the shank on both sides; and traditional therapy was prescribed. A follow-up examination dd November 7, 2022 demonstrative positive laboratory changes: significantly reduced signs of inflammation (WBC: 4.33×10^9/L, albumin 29.6 g/L, CRP 0 mg/L). The therapy made it possible to eliminate acute phlebothrombosis and adduction contracture of the right lower limb; the patient was discharged in satisfactory condition, with improvements, for outpatient follow-up.

Currently, the patient is followed up by a traumatologist, rheumatologist; right hip replacement surgery is planned.

Discussion

Iliopsoas abscess is a rare disease which is difficult to diagnose even without any history of diseases. Long-lasting pain syndrome which hid the abscess made it impossible to timely diagnose a life-threatening condition. The value of this case study is that it demonstrates the importance of practitioner's attention to details in case of a long-lasting pain syndrome. During admission, the primary priority was intoxication syndrome, which was treated as a result of pneumonia, while the pain syndrome that persisted with slowly developing symptoms, required NSAIDs, tramadol, blocks and had an objective cause (posttraumatic coxarthrosis), was not taken into account. As the patient could not walk and lied for a majority of time, a comprehensive examination was challenging due to the marked pain syndrome, and a musculoskeletal infection was not suspected. Long-term NSAIDs which disguised the inflammatory process did not allow making the diagnosis sooner. In our clinical experience, we often face a situation when symptomatic treatment disguises manifestations of severe diseases. This case study demonstrates that a long-lasting pain syndrome should be taken seriously, and the situation should be treated from a different perspective every time the patient asks for help.

Conclusion

Iliopsoas abscess should be included in differential diagnosis in patients with fever, leg pain, antalgic gait with limited lip movement, and positive psoas symptom. Instructing medical professionals in the signs of iliopsoas abscess is essential for timely diagnosis of this life-threatening condition.

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ИДИОПАТИЧЕСКАЯ ЛЕГОЧНАЯ ГИПЕРТЕНЗИЯ И ТРОМБОЭМБОЛИЯ IN SITU: ТРУДНЫЙ СЛУЧАЙ В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Idiopathic Pulmonary Hypertension and in Situ Thromboembolism: A Difficult Case in Clinical Practice

Резюме

Легочная гипертензия представляет собой сложный для дифференциальной диагностики синдром, являющийся исходом различных патологических состояний. При исключении двух наиболее распространенных причин развития легочной гипертензии, таких как патологии левых камер сердца и тромбоэмболии легочной артерии, дальнейший поиск этиологии зачастую становится проблематичен. Несмотря на появление ряда международных и отечественных рекомендаций, а также определенные успехи в медикаментозной терапии, долгосрочный прогноз у пациентов с легочной артериальной гипертензией остается неблагоприятным. Представлен клинический случай пациентки, 39 лет, страдающей идиопатической легочной артериальной гипертензией (иЛАГ). Пациентка не могла выносить ребенка; все ее попытки, продолжительностью более 19-ти лет, оставались безуспешными. У данной пациентки наблюдалось «подострое» течение легочной артериальной гипертензии и достаточно быстрое прогрессирование заболевания со значительным ухудшением качества жизни, что повлекло за собой невозможность вынашивания беременности. Также имелись признаки, негативно влияющие на прогноз, такие как нарастание одышки, потери сознания, значительное снижение работоспособности и высокая степень легочной артериальной гипертензии (по данным эхокардиографии систолическое давление в легочной артерии (СДЛА) составило более 128 мм ртутного столба). В связи с неэффективностью стандартной терапии селективным ингибитором циклогуанозинмонофосфат (цГМФ) — специфической фосфодиэстеразы 5-го типа (ФДЭ5) — силденафилом; был рассмотрен вариант лечения двойной специфической терапией, что позволило изменить ситуацию, получить положительную динамику и определить акушерско-гинекологический прогноз.

Ключевые слова: *идиопатическая легочная артериальная гипертензия, экстракорпоральное оплодотворение, легочная артерия, правый желудочек, специфическая терапия*

Конфликт интересов

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

Источники финансирования

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Abstract

Pulmonary hypertension is a complex syndrome for differential diagnosis, which is the outcome of various pathological conditions. With the exclusion of the two most common causes of pulmonary hypertension, such as pathology of the left heart chambers and pulmonary embolism, further search for etiology often becomes problematic. Despite the emergence of a number of international and domestic recommendations, as well as certain successes in drug therapy, the long-term prognosis in patients with pulmonary arterial hypertension remains unfavorable. In the description of this clinical case in a 39-year-old woman suffering from idiopathic pulmonary arterial hypertension, the main complaint of the patient was very non-specific. The woman could not bear the child, all her attempts, lasting more than 19 years, remained unsuccessful. Even in absolutely healthy women, pregnancy is associated with the highest risks and is a powerful "test" of the body, not to mention patients suffering from rare diseases. The patient has a "subacute" course and a fairly rapid progression of the disease with a significant deterioration in the quality of life, which led to the impossibility of carrying a pregnancy. There were also signs that aggravated the prognosis, such as increased dyspnea, loss of consciousness, a significant decrease in working capacity and a high degree of pulmonary hypertension (according to echocardiography, systolic pressure in the pulmonary artery > 128 mm Hg). Due to the ineffectiveness of standard therapy with a selective inhibitor of cycloguanosine monophosphate — specific phosphodiesterase type 5 — sildenafil; the option of specific therapy for pulmonary hypertension was considered, which made it possible to change the situation and bring the patient into a stable state and draw conclusions about the pregnancy.

Key words: *idiopathic pulmonary hypertension, in vitro fertilization, pulmonary artery, right ventricle, specific therapy*

Conflict of interests

The authors declare no conflict of interests

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BNP — brain natriuretic peptide; FBG — fibrinogen; FV — factor V Leiden mutation; ITGA2 — integrin-alpha-2; MTRR — methionine -synthase-reductase; MTR — methionine synthase; NT-proBNP — N-terminal pro B type natriuretic peptide; PAI-I — plasminogen activator inhibitor-1; CCB — calcium channel blockers; VRT — vasoreactive test; iPAH — idiopathic pulmonary arterial hypertension; PA — pulmonary artery; PAH — pulmonary arterial hypertension, PH — pulmonary hypertension; LV — left ventricle; PV — pulmonary valve; PVR — pulmonary vascular resistance; MRI — magnetic resonance imaging; INR — international normalised ratio; RV — right ventricle; PASYS — pulmonary artery systolic pressure; TV — tricuspid valve; PATE — pulmonary artery thromboembolia; FDE-5 — phosphodiesterase, type 5; CTEPH — chronic thromboembolic pulmonary hypertension; CVP — central venous pressure; cGMP — cyclic guanosine monophosphate; IVF — in vitro fertilisation; ERA — endothelin receptor antagonists; echo-CG — echocardiography; EEG — electroencephalography

Relevance

Idiopathic pulmonary arterial hypertension (iPAH) is a severe chronic and rapidly progressing disease characterised by an increase in pulmonary vascular resistance (PVR) as a result of a number of pathogenic processes in the vascular wall, that causes obstructive remodelling of small pulmonary arteries and arterioles. [1] Idiopathic arterial hypertension accounts for a minor number of all pulmonary hypertension (PH) cases. Median survival of patients with idiopathic pulmonary arterial hypertension before PAH-specific therapy is 2.8 years, and the period from disease manifestation to final diagnosis is 2 to 3 years. [2]. Idiopathic arterial hypertension is an orphan disease; however, there are no accurate global epidemiological data [6]. The international registries show that iPAH morbidity is 0.9–7.6 per million people, whereas the incidence rate is 5.6–26 per million of people. Pulmonary artery thromboembolia or thrombosis in situ can be a result of impaired clotting cascade, including endotheliocyte and platelet dysfunction. Platelet pathology and pro-coagulation changes can have a role to play in formation of local thromboses in chronic thromboembolic pulmonary hypertension (CTEPH) [4]. Current PAH-specific therapy aims to restore the balance of vascular mediators (nitrogen oxide, prostacyclin, endothelin) — main pathogenic links in the development of pulmonary arterial hypertension [3]. Clinicians use 5 classes of products: endothelin receptor antagonists (ERA), type 5 phosphodiesterase inhibitors, soluble guanylate cyclase stimulants, prostacyclin analogues and prostacyclin receptor agonists [3]. Management of patients with pulmonary arterial hypertension involves regular assessment of therapy efficacy, after which a dose escalation and two or three products from various classes can be required, especially for patients with intermediate or high risk of death [5, 7].

This article describes a case study of a patient with idiopathic pulmonary hypertension, thrombosis in situ, which are induced by miscarriages and ten procedures of in vitro fertilisation (IVF) and are refractory to standard therapy with selective cyclic guanosine monophosphate (cGMP) inhibitor — specific type 5 phosphodiesterase, and diuretics.

Outpatient and inpatient medical records of the patient with pulmonary arterial hypertension were analysed retrospectively. On March 28, 2022, a 39-year-old

woman was referred for the first time to the cardiologist at Voronezh Regional Cardiology Dispensary (at the Budgetary Healthcare Institution Voronezh Regional Clinical Hospital No. 1) from the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Hospital No. 11, where primary healthcare providers had unsuccessfully attempted to control the patient's condition. (Fig. 1) The woman complained of shortness of breath after ascending just 3–4 stairs (1 flight of stairs), walking for up to 10 m, during household chores, also of swollen legs, dizziness, blood pressure fluctuations between 140/90 mm Hg and 90/70 mm Hg, episodes of rhythmic tachycardia up to 90–100 bpm, episodes of fainting.

Medical history: the patient considers herself ill from 2009, after the third miscarriage (pre-syncope was observed: dizziness, "congested" back of the head). From summer 2020, she has been having syncopal condition (several times a year) during physical load, forward bends, during hot weather. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) did not show any pathologies; however, the neurologist diagnosed syncope with spastic component due to arterial hypertension and hyperventilation. At the same very moment, the patient noted reduced tolerance to physical loads. In February 2021, examinations during her fourth pregnancy (in vitro fertilisation (IVF)) revealed changes in trombophilia gene polymorphism, Leiden mutation; the patient was prescribed enoxaparin sodium and acetylsalicylic acid. The patient had miscarriage at week 15–16 of gestation. By December 2021, she had 8 unsuccessful IVF procedures. During a routine examination in summer 2021, echocardiography showed enlarged pulmonary heart ***for the first time***. In December 2021, the patient underwent a ninth IVF procedure. In January 2022, she had hysteroscopy, after which the patient noted significant deterioration in her condition, episodes of syncope became more frequent (5 episodes in January–March 2022), worsened shortness of breath (even at minimal physical loads, e.g. body twists in bed), swollen legs.

Life history: no family history of cardiovascular diseases. Comorbidities: inherited multiple-factor trombophilia caused by factor V Leiden mutation (FV), heterozygous variant, methionine synthase (MTR), heterozygous variant, methionine -synthase- reductase (MTRR), homozygous variant, fibrinogen (FBG), heterozygous variant, plasminogen activator inhibitor-1

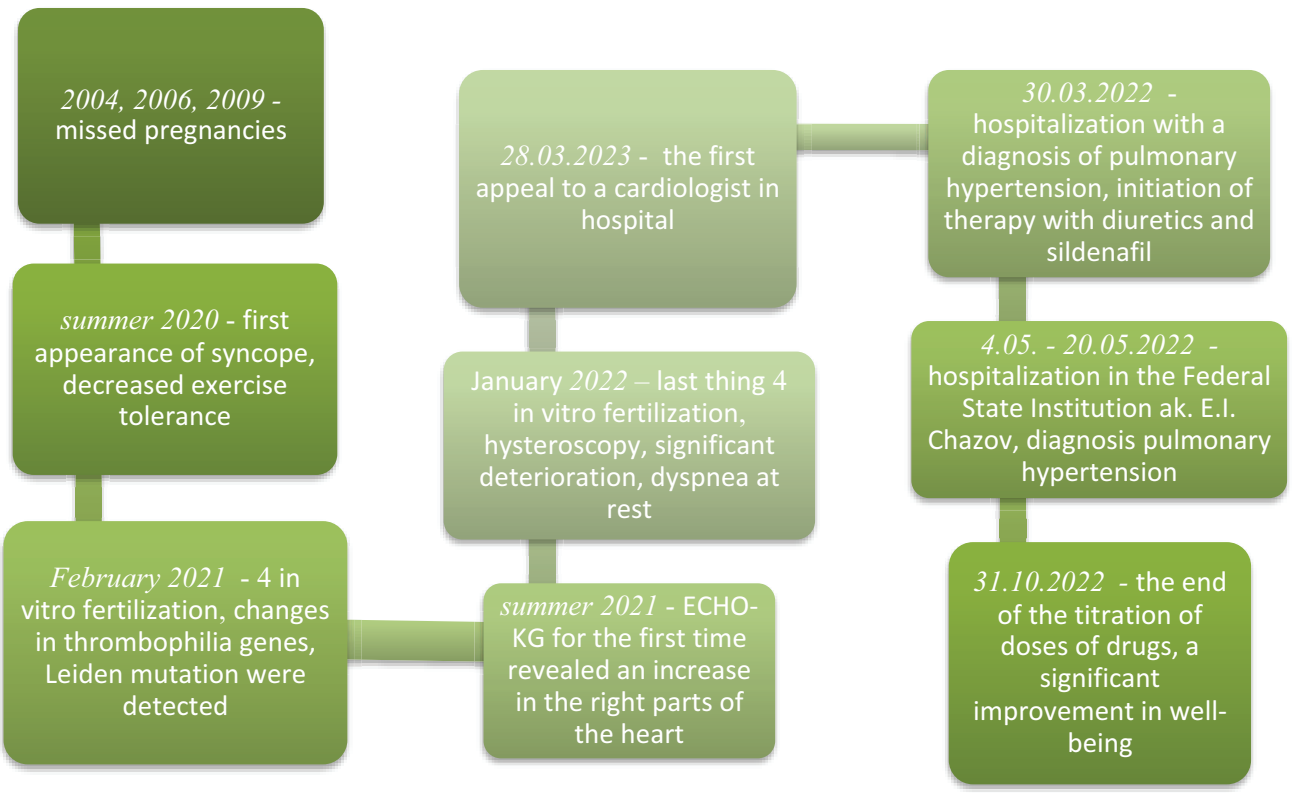


Figure 1. *Chronology of events*
Note: ECHO-KG — echocardiography

(PAI-I), heterozygous variant, integrin-alpha-2 (ITGA2), homozygous variant (diagnosed in 2020 during the fourth IVF procedure). Concomitant pathologies included superficial gastritis, reactive duodenitis, esophagitis. Mild obstructive apnoea syndrome was diagnosed in April 2022 after cardiorespiratory monitoring. Compensated chronic Hashimoto's thyroiditis (Euthyrox 125–150 μg daily). After unsuccessful attempts to conceive and carry pregnancy to term naturally (in 2004, 2006, 2009: missed miscarriages at weeks 5–6 of pregnancy), in 2020–2022 the patient was treated in the Budgetary Healthcare Institution of the Voronezh Region Voronezh Center for Family Health Protection and Reproduction, where the patient had 9 unsuccessful in vitro fertilisation procedures (from February 2021 to January 2022). History of allergies: acute essential oedema after ceftriaxone (as a child). TB, hepatitis B, C, human immunodeficiency virus, diabetes mellitus, typhus, paratyphoid fever, psoriasis, cancer — denies. No blood transfusions. Smoking and alcohol consumption — denies.

After an outpatient consultation by the cardiologist (March 28, 2022) due to conditions deterioration, the patient was referred to computed tomography angiography, which showed signs of pulmonary artery thromboembolia (PATE) in small branches on both sides. The patient was hospitalised to the Cardiac Defect Surgery Department of the Budgetary Healthcare Institution Voronezh Regional Clinical Hospital No. 1 with the diagnosis "thromboembolia of small branches of pulmonary artery (March 30, 2022). Circulatory inefficiency 2A. Functional class 3. High pulmonary hypertension. Trombophilia gene polymorphism (inherited multiple-factor thrombophilia caused by factor V Leiden mutation (FV), heterozygous variant, methionine synthase (MTR), heterozygous variant, methionine-synthase-reductase (MTRR), homozygous variant, fibrinogen (FBG), heterozygous variant, plasminogen activator inhibitor-1 (PAI-I), heterozygous variant, integrin-alpha-2 (ITGA2), homozygous variant" (from March 30 to April 6, 2023). After initiation of inpatient diuretic therapy (torasemide 5 mg daily, spirolacton 50 mg daily) and specific therapy (cyclic guanosine monophosphate inhibitor — type 5 phosphodiesterase (sildenafil) 20 mg three times daily), the patient noted short-term improvement in her health condition. Anticoagulant therapy with warfarin was prescribed. No surgery for pulmonary artery thromboembolia (PATE) was performed. The patient was consulted by pulmonologist, neurologist, somnologist. Under the recommendation of pulmonologist, the patient was referred for a consultation to the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of the Russian Federation (Moscow) (Pulmonary Hypertension Department) for differential diagnosis of iPAH and chronic thromboembolic pulmonary hypertension (CTEPH) (Table 1), as well as therapy adjustment.

The patient was hospitalised to the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of Russia from May 4 to May 20, 2022, where she underwent the following laboratory tests and instrumental examinations:

Complete blood count dd May 5, 2022: WBC — 9.8×10^9/L (N: 4.8–10.8); NEU — 5.3 K/μL (N: 1.9–8.0); LYMPH — 3.5 K/μL (N: 0.9–5.2); MON — 0.75 K/μL (N: 0.20–1.00); EOS — 0.14 K/μL (N: 0.00–0.80); BAS — 0.05 K/μL (N: 0.00–0.20); RBC — 4.36×10^{12}/L (N: 4.20–5.40); Hb — 12.80 g/dL (N: 12.00–16.00); HCT — 37.6 % (N: 37.0–47.0); mean corpuscular volume — 86.2 fL (N: 81.0–99.0); mean corpuscular haemoglobin — 29.4 pg (N: 27.0–31.0); mean corpuscular hemoglobin concentration — 34 g/dL (N: 33–37); RBC anisotropy factor — 14.5 % (N: 11.5–14.5); platelets — 345 $\times10^9$/L (N: 130–400); mean platelet volume — 10.3 fL (N: 7.2–11.1); PCT — 0.34 % (N: 0.02–1.00).

Blood biochemistry dd May 5, 2022: total bilirubin — 25.7 μmo/L (N: 1.7–20.5); K — 4.4 mmol/L (N: 3.5–5.3); Cl — 108.0 mmol/L (N: 98.0–108.0); Na — 139.0 mmol/L (N: 138.0–153.0); creatinine — 74.1 μmol/L (N: 50.0–98.0); K — 4.7 mmol/L (N: 3.5–5.3); Cl — 106.0 mmol/L (N: 98.0–108.0); Na — 142.0 mmol/L (N: 138.0–153.0).

D-dimer quantification dd May 5, 2022: D-dimer — 0.47 μg/mL (N: 0.00–0.50).

NT-proBNP (N-terminal pro B type natriuretic peptide) dd May 5, 2022): 1,893.0 pg/mL (N: 0.0–150.0).

Coagulation profile dd May 5, 2022: prothrombin time — 18.4 s (N: 5.0–15.0); international normalised ratio — 1.66 (N: 0.80–1.27); Quick's value — 49.0 % (N: 70.0–130.0).

Coagulation profile dd May 9, 2022: prothrombin time — 28.5 s (N: 5.0–15.0); international normalised ratio — 2.50 (N: 0.80–1.27) (patient was prescribed warfarin 5 mg).

Urinalysis dd May 5, 2022: colour — yellow; acidity — 5.5/faintly acid (N: 5.0–7.0); protein — 0.10 g/L; glucose — 0.3 mmol/L (N: 0.0–0.8); ketone bodies — neg (N: 0–1); bilirubin — neg; urobilinogen — 0 μmol/L (N: 0–34), squamose epithelium — 1 cell/μL (N: 0–28); WBC — 10 cell/μL; non-lysed RBC — 4 cell/μL; mucus — little per HPF; specific gravity — 1,023; clarity — completely clear.

Table 1. Classification of pulmonary hypertension, necessary for the standardization of diagnostic and treatment approach

Group 1 Pulmonary arterial hypertension	Refers to the number of orphan diseases. Clinical features: younger patients, family history, risk factors, associated diseases ECG: Rotation of the electrical axis to the right, hypertrophy of the pancreas. ECHO-KG: the right ventricle is enlarged, the right atrium is larger than the left atrium, the interventricular septum is deflected to the left, the transmitral blood flow is E/A ≤ 1, the Dopplerogram of the lateral segment of the fibrous ring of the mitral valve is E/Em < 8. X-ray of the chest organs: enlargement of the right chambers, dilated pulmonary artery, depletion of pulmonary blood flow in the periphery. Biomarkers: BNP/NT-proBNP — increased. Perfusion lung scintigraphy in combination with ventilatory lung scintigraphy: used to rule out chronic thromboembolism. Transventional cardiac catheterization: pulmonary artery wedge pressure ≤ 15 mm Hg, pulmonary-vascular resistance> 3 units. Wood, diastolic pulmonary gradient >7 mm Hg. Treatment: we have the right to prescribe specific therapy (but only idiopathic pulmonary hypertension is included in the federal list of orphan diseases).
Group 2 Pulmonary hypertension associated with pathology of the left chambers of the heart	Clinical features: older patients, arterial hypertension, diabetes mellitus, coronary artery disease, body mass index > 30 kg/m^2, clinical picture of congestive heart failure, history of cardiac asthma/pulmonary edema, orthopnea. ECG: Rotation of the electrical axis to the left, left ventricular hypertrophy, atrial fibrillation. ECHO-KG: the right ventricle can be enlarged, the left atrium is enlarged, the interventricular septum is deflected to the right, the transmitral blood flow E/A > 1, Dopplerogram of the lateral segment of the fibrous ring of the mitral valve E/Em > 10. Chest X-ray: congestive changes in the lungs, Kerley lines, pleural effusion, enlargement of the left chambers of the heart. Biomarkers: BNP/NT-proBNP — increased. Perfusion pulmonary scintigraphy in combination with ventilatory pulmonary scintigraphy: used to rule out chronic thromboembolism. Transventional cardiac catheterization: pulmonary artery wedge pressure > 15 mm Hg., diastolic pulmonary gradient < 5 mm Hg.
Group 3 Pulmonary hypertension bound with lung disease and/or hypoxia	Causes: chronic obstructive pulmonary disease, interstitial lung disease, other lung diseases with mixed restrictive and obstructive disorders, hypoxia in the absence of lung disease, respiratory disorders during sleep, alveolar hypoventilation syndrome, high-altitude pulmonary hypertension, abnormal development of the lungs. Perfusion lung scintigraphy is used in combination with ventilation lung scintigraphy.
Group 4 Pulmonary hypertension due to obstruction of the pulmonary arteries	Causes: chronic thromboembolic pulmonary hypertension, other pulmonary artery obstructions (angiosarcoma, other intravascular tumors, arteritis, congenital anomalies, parasitic diseases) Perfusion lung scintigraphy is used in combination with ventilation lung scintigraphy Treatment: thromboendarterectomy is indicated for patients with chronic thromboembolic pulmonary hypertension.
Group 5 Pulmonary hypertension of unknown or mixed origin	Causes: hematological diseases (chronic hemolytic anemia, myeloproliferative diseases, splenectomy), systemic disorders (sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis), metabolic disorders (glycogenosis, Gaucher disease) and others. Treatment: more often surgical — thromboendarterectomy, atrial septostomy is indicated for patients with valvular heart disease.

Note: BNP — brain natriuretic peptid, ECG — electrocardiography, ECHO-KG — echocardiography, NT-proBNP — N-terminal pro-brain natriuretic peptid. [Avdeev S.N., Barbarash O.L., Bautin A.E., et al. 2020 Clinical practice guidelines for Pulmonary hypertension, including chronic thromboembolic pulmonary hypertension. Russian Journal of Cardiology. 2021;26(12):4683. https://doi.org/10.15829/1560-4071-2021-4683].

Electrocardiogram dd May 4, 2022: sinus tachycardia, 109 bpm. Electric axis deviation to the right. Signs of myocardial changes as a result of right ventricle hypertrophy.

Chest X-ray dd May 5, 2022: changes are consistent with high pulmonary arterial hypertension. Enlarged pulmonary heart. Delated azygous vein.

Echocardiography (M- и B-mode, colour Doppler imaging, Doppler sonography) dd May 16, 2022: dilated right heart with signs of right ventricle (RV) pressure overload. Dilated pulmonary trunk and branches. Ejection fraction 60 % (Simpson's). Right ventricular (RV) myocardial hypertrophy. Hight pulmonary arterial hypertension (94–99 mm Hg). Moderately reduced systolic function of right ventricle (RV). Tricuspid valve (TV) insufficiency, grade 2–3, pulmonary valve (PV) insufficiency, grade 1–2. Signs of moderately increased central venous pressure (CVP). Small amount of liquid in pericardial cavity.

Abdominal ultrasound dd May 5, 2022: slightly enlarged liver due to left lobe thickness. Spleen: unremarkable. Moderate diffuse changes in liver and pancreas parenchyma. Ultrasound signs of venous stasis in the system of inferior vena cava. No ultrasound signs of portal hypertension, abdominal dropsy. Ultrasound signs of chronic calculous cholecystitis.

Holter ECG monitoring dd May 6, 2022 — May 7, 2022: 24-hour ECG monitoring recorded sinus rhythm with 90 bpm (minimal heart rate is 70 bpm at 04:30 am, maximum value is 133 bpm at 12:19 pm). 2 ventricular

extrasystoles, single supraventricular premature beat. Changes in ST segment cannot be assessed to the initially modified terminal section of the ventricular complex.

Spirometry with computer-aided data processing dd May 6, 2022: lung capacity and airway patency are above the age norm.

High frequency focus ultrasound of peripheral arteries dd May 11, 2022: atherosclerotic plaques in the carotid not observed. Atherosclerotic plaques in femoral arteries not observed.

CT angiography of pulmonary arteries (MSCT-pulmonary angiography) dd May 11, 2022: no signs of massive thrombosis of pulmonary artery (PA) trunk and large branches. Signs of pulmonary hypertension. Thrombosis of some small subsegmental branches next to right C3 branch cannot be ruled out. A hypodense mass in left adrenal gland; probably, an adenoma.

Duplex scanning of iliofemoral veins dd May 13, 2022: saphenofemoral junctions are not dilated on both sides, no signs of thrombosis, ostial valves are intact. Blood flow in both common femoral veins is phasic, synchronised with breath.

Perfusion lung scintigraphy dd May 16, 2022: scintigraphic signs of pulmonary hypertension; no signs of focal perfusion changes in lungs and right-to-left shunt.

After a comprehensive clinical and laboratory examination (including pulmonary heart catheterisation) at the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of Russia, the purpose of which was to find the origin of pulmonary hypertension, there were no data evidencing pulmonary hypertension caused by left heart pathology, congenital heart disorder, lung pathology, chronic thromboembolic pulmonary hypertension. The patient was diagnosed with idiopathic pulmonary hypertension with pulmonary artery thrombosis in situ, functional class III (according to WHO guidelines). Taken condition severity, low functional class, signs of blood flow insufficiency and factors of poor prognosis, the medical panel decided to adjust the PAH-specific therapy: cyclic guanosine monophosphate inhibitor — specific type 5 phosphodiesterase was replaced with riociguat at an initial dose of 0.5 mg three times daily, and selexipag was initiated at an initial dose of 200 μg twice daily. The patient tolerated both products without side effects. Later, it was recommended to titrate riociguat at 0.5 mg three times daily every 2 weeks up to the maximum dose of 2.5 mg three times daily (systolic blood pressure should be controlled before every medication intake), and weekly selexipag titration as per algorithm until the dose is 1,600 μg twice daily (Table 2). This therapy is life-saving; it cannot be replaced or discontinued. Taking into account the presence of idiopathic pulmonary hypertension, the patient was prescribed anticoagulant therapy with warfarin; considering thrombosis of some small subsegmental branches of pulmonary arteries, the target value of international normalised ratio (INR) is 2.5–3.5. Since the patient had sinus tachycardia, ivabradine was prescribed at an initial dose of 5 mg daily to maintain the heart rhythm. During the inpatient observation, the patient's condition remained stable, without circulatory inefficiency aggravations; blood pressure was 110–120/70–80 mm Hg. The patient was discharged in satisfactory condition.

Table 2. *Dose titration of of specific therapy for pulmonary hypertension (riociguat and selexipag)*

Дата/препарат Date/drug	мг в сутки/ mg per day	мкг в сутки/ mkg per day
	Риоцигуат/ Riociguat	Селексипаг/ Selexipag
25.07.2022	3,75	400
26.07.2022	3,75	400
27.07.2022	3,75	400
22.08.2022	6	400
23.08.2022	6	400
24.08.2022	6	400
05.09.2022	7,5	400
06.09.2022	7,5	400
07.09.2022	7,5	400
19.09.2022	7,5	800
20.09.2022	7,5	800
21.09.2022	7,5	800
26.09.2022	7,5	1200
27.09.2022	7,5	1200
28.09.2022	7,5	1200
03.10.2022	7,5	1600
04.10.2022	7,5	1600
05.10.2022	7,5	1600
10.10.2022	7,5	2000
11.10.2022	7,5	2000
12.10.2022	7,5	2000
17.10.2022	7,5	2400
18.10.2022	7,5	2400
19.10.2022	7,5	2400
24.10.2022	7,5	2800
25.10.2022	7,5	2800
26.10.2022	7,5	2800
31.10.2022	7,5	3200
01.11.2022	7,5	3200
02.11.2022	7,5	3200

Outpatient follow-up dd October 16, 2022: the patient does not complain of shortness of breath at rest and while speaking; shortness of breath appears at fluent speech and when ascending 10 and more stairs; she can tolerate household chores well; no syncope was observed.

Objective findings: the general condition is relatively satisfactory. The patient's consciousness is clear. Height: 167 cm. Weight: 82 kg. Body mass index: 29 kg/m^2 (overweight). Skin is of normal colour; mucous membranes are wet and of normal colour. The oropharynx is not hyperaemic. The subcutaneous fat layer is moderately developed; palpable lymph nodes are not enlarged. Breasts: visually unremarkable. Bones, joints and muscles: visually unremarkable. Thyroid gland: visually and palpatory unremarkable. Shank pastosity, more in the left shank.

6-min walk distance: pre-test SpO2 - 98 %, heart rate - 85 bpm; post-test SpO2 - 100 %, heart rate - 132 bpm. The patient walked 370 m. Borg Dyspnoea Scale: 5 points.

Respiratory system: the chest in normosthenic. Respiratory rate: 16 respirations per minute. Both hemithoraxes are evenly engaged in respiration; vocal fremitus is normal. Percussion sound is clear above all pulmonary fields; auscultatory vesicular respiration in all chest sections, without stridor. Shortness of breath on exertion is significant.

Circulation organs: the apex beat is in the 5th intercostal space along the left midclavicular line. Cardiac dullness border: right — at the right sternum edge; left — in the 5th intercostal space along the left midclavicular line; upper — in the 3rd intercostal space; the cardiac sound is clear; the loud second heart sound is above the pulmonary vein; diastolic murmur is in the auscultation point of tricuspid valve; the rhythm is regular, with a heart rate of 80 bpm; pulse: 80 bpm (no deficit); filling and exertion are normal. Blood pressure, right arm: 110/70 mm Hg, blood pressure, left arm: 114/70 mm Hg.

GIT: hearty appetite; the tongue is moist and clear; on palpation, the abdomen is soft and non-tender in all sections; the liver is palpable 1 cm below the right costal arch; spleen is not palpable; bowel movement: unremarkable.

Urinary system: urination is unobstructed; kidneys are not palpable; kidney punch is negative on both sides.

Neuropsychological status: memory is normal, the patient is lucid; sleep is normal; the patient understands her condition; no signs of severe disorders in 12 pairs of cranial nerves.

Sensory organs: eyesight, hearing and olfaction are normal.

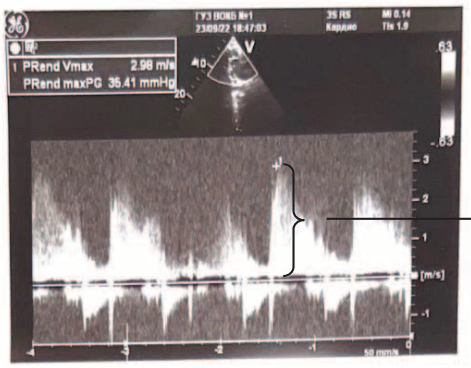
Based on clinical findings, results of laboratory and instrumental tests, the patient was diagnosed with the primary diagnosis "Idiopathic pulmonary hypertension. Functional class III (WHO). Thrombosis in situ of pulmonary arteries. Relative incompetence of tricuspid valve, grade 2–3, pulmonary artery valve insufficiency, grade 1–2. ***Complications.*** Chronic heart failure, grade IIB, NYHA functional class III. ***Comorbidities.*** Inherited multiple-factor thrombophilia caused by factor V Leiden mutation (FV), heterozygous variant, methionine synthase (MTR), heterozygous variant, methionine synthase reductase (MTRR), homozygous variant, fibrinogen (FBG), heterozygous variant, plasminogen activator inhibitor-1 (PAI-I), heterozygous variant, integrin-alpha-2 (ITGA2), homozygous variant. Superficial gastritis. Reactive duodenitis. Esophagitis. Mild obstructive apnoea syndrome. Chronic Hashimoto's thyroiditis".

The patient was recommended to modify her lifestyle: flu and pneumococcal disease vaccination; supplemental oxygen is recommended for air travel; in scheduled surgeries, epidural is preferable (not inhalation anaesthesia); excessive physical activity, changes of climatic regions and staying in high mountain regions should be avoided, as they can cause clinical deterioration. Also, a healthy diet is recommended: animal fats and cholesterol-rich products should be limited; spicy, fried and smoked products as well as easily digested carbohydrates should be avoided. Daily water intake should not exceed 1.2–1.3 L. Monitoring of consumed fluid and urination, weight monitoring. Sodium chloride consumption should be limited to 3 g/day; optimal work and rest schedule, limited emotional and physical load, which can cause condition decompensation. The most important recommendation for the patient was that, due to a high risk of complications, pregnancy is absolutely contraindicated. The patient was strongly encouraged to use barrier contraception; she was consulted by a psychologist. A professional psychologist noted positive changes and acceptance by the patient of her chronic condition, adherence to treatment is satisfactory.

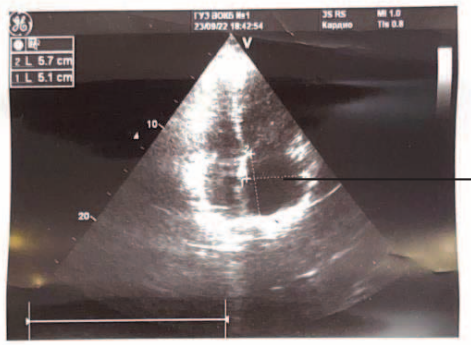
The following medicinal products are recommended permanently: selexipag 200 mg twice daily (riociguat during titration); riociguat 1 mg three times daily, the dose should be increased bu 1.5 mg/day every 2 weeks (0.5 mg for each intake) up to a dose of 2.5 mg three times daily (up to 7.5 mg/day); warfarin 2.5 mg 2 tablets daily with INR monitoring; furosemide 40–80 mg to be alternated with torasemide 20 mg (with daily weight and diuresis monitoring; electrolytic profile (K, Na) monitoring once every 3 weeks) (this diuretic therapy regimen was selected and titrated during hospitalisation

at the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of Russia); ivabradine 5 mg (1 tablet) in the morning and 2.5 mg (half a tablet) in the evening; if required, 5 mg (1 tablet) in the evening (with heart rate monitoring); spironolactone 100 mg daily.

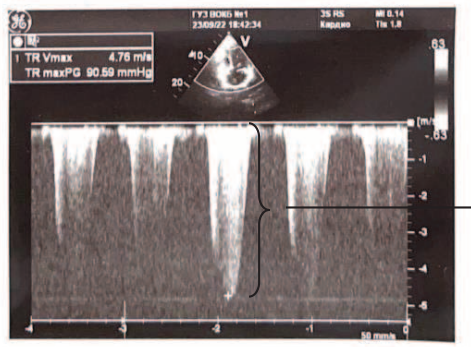
During the six-month follow-up after verification of the final clinical diagnosis and prescription of PAH-specific therapy (it is well tolerated), the patient's condition stabilised, disease activity decreased. The clinical presentation comprised disappearance of dyspnoea at rest, reduced dyspnoea during physical activity; episodes of syncope disappeared after completion of medicinal product titration. Once the general condition stabilised, the patient was referred to the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Centre for Exercise Therapy and Sport Medicine 'Rehabilitation' for training under supervision of a rehabilitation physician, where she had a set of special exercises with soft physical load and elements of yoga. Laboratory and instrumental tests demonstrated some positive results: NT-proBNP reduced to 243.0 pg/mL (dd November 29, 2022), pulmonary artery pressure reduced to 90 mm Hg, regurgitation in pulmonary valve corresponds to grade 1 (echocardiography dd September 23, 2022) (Figure 2).



The pressure in the outflow section of the right ventricle is 35 mm Hg.



Right atrium 51 mm x 57 mm



Peak velocity of tricuspid regurgitation - 4.76 m/s

Figure 2. *Echocardiography data of patient P, 40 years old, dated from 09/23/2022 y.*
Note: Dilatation of the right chambers is noted. Ejection fraction 62 % (according to Simpson). Hypertrophy of the right ventricular myocardium. High arterial pulmonary hypertension. Right ventricular systolic function is moderately reduced. The pumping function of the left ventricle isn't reduced. Insufficiency of the tricuspid valve 2-3 degrees, pulmonary valve 1 degree

Discussion

Chronic conditions in women of reproductive age can negatively affect the course and outcome of pregnancy; however, they are not an absolute contradiction for having a baby. Modern healthcare makes it possible for women with multiple, sometimes severe, conditions to have a term pregnancy and healthy children. However, high pulmonary hypertension syndrome is *an exception*. Scarce literature data indicate that recently the number of mothers lost to this pathology is 12–36 %. Diagnosis of high pulmonary hypertension in a patient is *an absolute contraindication* to pregnancy. Termination of pregnancy is mandatory both in first and second trimesters (especially for patients with an estimated pulmonary systolic pressure of over 50 mm Hg) [14]. Pregnant women with high PH account for 0.54 % of all hospitalised patients with cardiovascular diseases. Maternal mortality in PAH reaches 56 % [11]. Mortality in patients with pulmonary circulation hypertension during pregnancy and immediately after birth is very high (material mortality) (in primary pulmonary hypertension — 30–40 %; in Eisenmenger's syndrome — 30–60 %) [14].

Literature reviews present the global experience with management of female patients with PH of functional class 1 and 2 during pregnancy and postpartum period. According to a majority of experts, female patients with this pathology (especially of high risk, functional class 3–4) are strongly encouraged to undergo sterilization or use a reliable method of contraception, and if a woman becomes pregnant, pregnancy must be terminated [12]. That is why it is very important to inform women with pulmonary hypertension about risks associated with pregnancy and provide them with recommendations from a woman health specialist and an expert in PH regarding adequate contraception [13]. Also, it is essential to take into account that a majority of PAH-specific medications can cause deformities and congenital abnormalities [1].

In this case study, it is undeniable that numerous pregnancies contributed to manifestations of pulmonary hypertension symptoms, which caused deterioration of general condition and functional class of PAH. In recurrent miscarriages, healthcare professionals should include pulmonary hypertension into a differential diagnosis [1,13,15]. Also, taken a high risk of PH progression during pregnancy, it is absolutely unacceptable to plan and maintain pregnancy in patients with an expected systolic pulmonary pressure of over 50 mm Hg. [15].

Unlike common diseases, in which risk identification and classification, treatment and observation are performed by primary healthcare providers, delivery of care to patients with a rare pathology, including pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, requires involvement of specialists, who are not only aware of the problem, but also have practical experience in management of such conditions. An efficient solution can be cardiovascular risk management centres operating at tier 3 (specialised) medical institutions [10]. For a number of regions, these will be centres for cardiac failure or rare diseases, where specifically trained specialists in PH can render their services. An advantage of such an approach is a possibility to form a multidisciplinary team, which decides on an optimal management of a patient with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. At the next routing stage (tier 3 specialised centres), results of examinations and tests performed in a regional medical institution as part of specialised medical assistance, where PAH or CTEPH is suspected, are forwarded to a federal expert centre, using telemedicine technologies [10] (in this case, the patient was referred to the Federal State Budgetary Institution E. I. Chazov National Medical Research Institute of Cardiology of the Ministry of Health of the Russian Federation in Moscow, Pulmonary Hypertension Department).

Current management approach for patients with PAH is aimed at reduction of mortality; in other words, the aim is to achieve the low PAH functional class (I–II), good tolerability of physical activities, low NT-proBNP levels (< 330 ng/L) and absence of any signs of right ventricle dysfunction. The management strategy for patients with PAH can be divided into three stages. According to the current Russian guidelines, patients should be included into special rehabilitation programs in order to improve their physical condition. Stage one includes general measures: discussion of routine physical activity, family planning, contraception and postmenopausal hormone replacement therapy, preparation for scheduled surgeries, infection prevention, psychological and social support, ability to travel and therapy compliance [1]. Also, maintenance therapy (oxygen therapy, diuretics, digoxin) and follow-up by specialists from a PH centre are required, where catheterisation of the pulmonary heart can be performed for continuous monitoring of therapy efficiency. Since patients with PAH often have depression, psychological and social rehabilitation and classes for clinical and psychological

adaptation are required in order to reduce the risk of anxiety and depression [9].

According to the current Russian guidelines, there are two components of the drug therapy for patients with PAH: maintenance therapy (indirect anticoagulants (vitamin K antagonists), diuretics, cardiac glycosides, oxygen therapy) and specific therapy, including calcium channel-blocking agents (CCB), antihypertensive agents for pulmonary arterial hypertension (bosentan, macitentan, ambrisentan), iloprost for inhalation, phosphodiesterase inhibitors (iFDE-5), riociguat and selexipag [1].

Stage two is PAH-specific therapy with high doses of calcium channel blockers in patients with positive vasoreactive test (VRT) or with approved PAH medications in patients with negative test results. This recommendation is applicable to patients with idiopathic pulmonary arterial hypertension.

Stage three is associated with response to therapy, determination of comprehensive therapy with approved drugs or presence of indications for lung transplantation [9].

According to the theory of PAH development, simultaneous impact on various paths of pathogenesis can not only prevent disease progression, but also can make it possible to manage the outcomes more efficiently [3]. Modern PAH-specific medications have not only vasodilatory effect, but also a number of other actions — cytoprotective, antiproliferative, antiaggregatory, etc. Riociguat belongs to a new drug class, soluble guanylate cyclase stimulants [4]. Selexipag is the only non-prostanoid selective IP-receptor protagonist, an oral drug [8]. These drugs, if titrated correctly and provided the highest individual maintenance dose is achieved, result in vasorelaxation, inhibition of proliferative, inflammatory and fibrous effects.

PAH-specific therapy initiated in this case study at the federal expert centre stabilised the patient's condition (blood pressure and heart rate, circulatory inefficiency). This is a combination of a selective IP-receptor protagonist (selexipag) and a soluble guanylate cyclase stimulant (riociguat), titrated to their target values, that improved the patient's quality of life.

In addition to drug therapy, patient rehabilitation is important as well. In 2017, N. R. Morris et al. conducted a meta-analysis of the impact of physical rehabilitation on physical capability and quality of life of patients with PAH, who were prescribed adequate specific therapy with antihypertensive drugs for PAH management. Physical rehabilitation programs included aerobic exercises, power load, breathing exercises and elements of yoga [1]. Our patient was also provided with recommendations for physical activities. The patient decided to take classes with a specialist from the Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Centre for Exercise Therapy and Sport Medicine 'Rehabilitation', and she noted improvements both in her physical, mental and emotional state.

Conclusions

This case study demonstrates advisability of a complex clinical and laboratory assessment (including pulmonary heart catheterisation) in order to clarify the aetiology of pulmonary hypertension and decide whether PAH-specific therapy is required. Comprehensive therapy of pulmonary hypertension uses maintenance therapy, that does not impact the survival rate of patients with pulmonary hypertension, and specific drugs, the use of which prolongs the patient's life, reduces the number of hospitalisations and prolongs the period to clinical deterioration and transplantation. Timely therapy initiation after the final clinical diagnosis improves the long-term prognosis for patients with PAH. Pregnancy in women with pulmonary hypertension is of specific interest. However, unfortunately, at this stage, the modified WHO classification states: in terms of the risk of cardiovascular complications for the mother and children, pregnant women with PH are included in risk category IV, and we can claim that pregnancy is very dangerous for patients with PH. Pregnancy planning and carrying should be discussed and decided by an obstetrician-gynaecologist together with a cardiologist. Pregnancy is a risk for women with any pulmonary hypertension, especially with idiopathic PAH, because it is associated with high maternal mortality. Therefore, women with PH are recommended to use reliable contraception to prevent pregnancy or to consider immediate pregnancy termination, in order to prevent pulmonary hypertension progression and deterioration.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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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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Международная (Всероссийская) практическая медицинская конференция студентов и молодых учёных Гаазовские чтения: «Спешите делать добро…» — это ежегодная конференция, посвященная разбору клинических случаев.

Идея проведения Гаазовских чтений была сформулирована деканом международного факультета и председателем оргкомитета конференции **Надеждой Александровной Быловой**: «*В обучении студентов медицинского вуза и в работе студенческого научного кружка разбор клинических случаев имеет большое значение. Это, в первую очередь, помогает будущим врачам подготовиться к клинической практике. Главное преимущество формата Гаазовских чтений заключается в возможности подготовить доклад в относительно короткие сроки. При этом участники конференции проводят большую работу по поиску информации о возможных методах диагностики и лечения описываемой ими патологии, исторических данных о заболевании, дифференциальной диагностике и оценке прогноза пациентов. Разбор клинических случаев неизменно вызывает большее количество вопросов и более подробное обсуждение, чем разбор научной работы*».

В этом году XIII Международная (XVIII Всероссийская) практическая медицинская конференция студентов и молодых учёных Гаазовские чтения «Спешите делать добро…» состоялась 23 и 24 декабря 2023 года на онлайн-площадке РНИМУ им. Н.И. Пирогова.

В этом году она традиционно собрала студентов и молодых учёных из разных российских и зарубежных медицинских вузов.

Председатель оргкомитета конференции декан международного факультета Университета **Надежда Александровна Былова** во вступительном слове рассказала о важности разбора клинических случаев и интересе конференции не только для студентов и молодых ученых, но и для врачей с большим опытом.

Секционные чтения проходили по четырём направлениям: 23 декабря «Детская хирургия» и «Педиатрия», а 24 декабря «Хирургия» и «Терапия». Уникальность формата этой конференции заключается в том, что докладчики представляют вниманию аудитории интересные клинические случаи из своей врачебной практики.

Подводя итоги конференции, жюри поблагодарило участников за качественно подготовленные тезисы, а также оценило удобство дистанционного формата. **Елена Владимировна Резник**, д.м.н., профессор, заведующая кафедрой пропедевтики внутренних болезней ЛФ отметила, что многое почерпнула из докладов, что позиция молодых ученых и студентов уже является позицией настоящих врачей и профессионалов и что вопросы, которые задают члены жюри всегда являются поводом для дальнейшего совершенствования авторов докладов.

Вера Николаевна Ларина, профессор, заведующая кафедрой поликлинической терапии ЛФ, отметила, что данные чтения позволяют ежегодно развивать навыки разбора пациентов, узнавать о новых нозологиях, находить свои направления научной и практической деятельности.

В завершении конференции **Марина Владимировна Костюченко**, д.м.н., доцент профессор кафедры медицины катастроф ЛФ, обратилась к спикерам со словами благодарности и отметила высокий уровень докладов авторов секций «Хирургия» и «Терапия».

По итогам конференции призовые места распределились следующим образом:

Секция «Детская хирургия»:

- **I место: Калашников Алексей Андреевич,** Детская городская клиническая больница № 9 им. Г.Н. Сперанского, Научно-исследовательский клинический институт педиатрии и детской хирургии имени академика Ю.Е. Вельтищева, ХИРУРГИЧЕСКАЯ КОРРЕКЦИЯ СКОЛИОТИЧЕСКОЙ ДЕФОРМАЦИИ ПРИ МЕРОЗИН-НЕГАТИВНОЙ МЫШЕЧНОЙ ДИСТРОФИИ.
- **II место: Пилоян Феликс Самсонович, Сагоян Гарик Барисович, Баязитов Римир Радикович,** Национальный медицинский исследовательский центр здоровья детей, Национальный медицинский исследовательский центр онкологии имени Н.Н. Блохина, КЛИНИЧЕСКИЙ СЛУЧАЙ УСПЕШНОГО ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ В СОЧЕТАНИИ С ТАРГЕТНОЙ ТЕРАПИЕЙ У РЕБЕНКА С CLOVES-СИНДРОМОМ.
- **III место: Проплеткина Кристина Дмитриевна, Ванян Лиза Арамовна, Перевощикова Александра Сергеевна, Павлова Дарья Николаевна**, Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, СИНДРОМ КАУДАЛЬНОГО УДВОЕНИЯ У НОВОРОЖДЕННОГО РЕБЕНКА.

Секция «Педиатрия»:

- **I место: Дышева Анастасия Игоревна, Тулупова София Алексеевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, МЕТИЛМАЛОНОВАЯ АЦИДЕМИЯ, АССОЦИИРОВАННАЯ С АПЛАСТИЧЕСКОЙ АНЕМИЕЙ.
- **II место: Косничева Елена Алексеевна, Соколова Ксения Дмитриевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, КЛИНИЧЕСКИЙ СЛУЧАЙ МЕТГЕМОГЛОБИНЕМИИ.
- **III место: Гурина Наталья Борисовна, Мустайкин Сергей Николаевич, Зайцев Дмитрий Владимирович,** Минская областная детская клиническая больница, ВРОЖДЕННАЯ АПЛАЗИЯ КОЖИ ГОЛОВЫ, ОПЫТ КОНСЕРВАТИВНОГО ВЕДЕНИЯ ПАЦИЕНТА.

Секция «Хирургия»:

- **I место: Синельникова Софья Юрьевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, СИНДРОМ ВЕРХНЕЙ АПЕРТУРЫ ГРУДНОЙ КЛЕТКИ КАК ПРИЧИНА ТРОМБОЗА ГЛУБОКИХ ВЕН ВЕРХНИХ КОНЕЧНОСТЕЙ.
- **II место: Агабекян Гор Араикович, Мовсесян Диана Ашотовна, Галатонов Артем, Соловьев Даниил Антонович, Арутюнян Гамлет Арутюнович,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, ПЕРВАЯ ПЕРЕСАДКА ЛЕГКИХ ПАЦИЕНТКЕ С МУКОВИСЦИДОЗОМ: ОТДАЛЕННЫЕ РЕЗУЛЬТАТЫ.
- **II место: Астанова Нигина Бахтиёр кизи,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, КЛИНИЧЕСКИЙ СЛУЧАЙ ПАЦИЕНТА С ТЕРАТОМОЙ БРЫЖЕЙКИ ТОНКОЙ КИШКИ.
- **III место: Носкова Екатерина Максимовна, Панькова Надежда Николаевна, Абдуллаева Роза Рамик кызы, Мельникова Анна Сергеевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, ОН ЕЩЕ СМОЖЕТ ВАС УДИВИТЬ. КЛИНИЧЕСКИЙ СЛУЧАЙ МУКОЦЕЛЕ АППЕНДИКСА.

Секция «Терапия»:

- **I место: Ковальков Александр Владимирович, Морозова Вероника Николаевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, КЛИНИЧЕСКИЙ СЛУЧАЙ ЦЕНТРАЛЬНОГО ПОНТИННОГО МИЕЛИНОЛИЗА.
- **II место: Шубный Данила Павлович,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, ТРУДНОСТИ ДИАГНОСТИКИ СИНДРОМА ПИКЕРИНГА — РЕДКОГО ОСЛОЖНЕНИЯ СТЕНОЗА ПОЧЕЧНЫХ АРТЕРИЙ.
- **III место: Дмитриева Анастасия Павловна, Орехова Ксения Михайловна,** Ярославский государственный медицинский университет, ТРУДНОСТИ ДИАГНОСТИКИ ТУБЕРКУЛЕЗА У ПАЦИЕНТА 75 ЛЕТ.

Традиционный специальный приз от декана международного факультета был присужден двум молодым ученым:

1. **Башкатова Анастасия Андреевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, КЛИНИЧЕСКИЙ СЛУЧАЙ УСПЕШНОГО СИМУЛЬТАННОГО ЛЕЧЕНИЯ ПАЦИЕНТА С ОНКОЛОГИЧЕСКИМ ЗАБОЛЕВАНИЕМ, КРИТИЧЕСКИМ АОРТАЛЬНЫМ ПОРОКОМ СЕРДЦА И ИБС (секция «ХИРУРГИЯ»).
2. **Ковалёва Анастасия Алексеевна,** Российский Национальный Исследовательский Медицинский Университет им. Н.И. Пирогова, LMNA-КАРДИОМИОПАТИЯ У БОЛЬНОЙ С ПРОГРЕССИРУЮЩЕЙ МЫШЕЧНОЙ ДИСТРОФИЕЙ ЭМЕРИ-ДРЕЙФУСА (секция «ТЕРАПИЯ»).

Кроме того, отдельно оценивались доклады, представленные в постерном формате.

«Детская хирургия»

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«Хирургия»

I место: Коздоба Андрей Ильич, Андронатий Виктория Александровна, Зарипова Альмира Айдаровна
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РАЗНЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ АНЕВРИЗМ ПЕРИФЕРИЧЕСКИХ АРТЕРИЙ.

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ERYTHEMA PERNIOSIS — О ЦЕННОСТИ АНАМНЕЗА.

Желаем авторам докладов достижения профессиональных высот!

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