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С.Н. Маршала[1,2], М.Д. Яровой[1], Т.Я. Чернобровкина[1], И.В. Семенякин[2], Е.В. Резник[1,2,3]

[1] — ФГАОУ ВО «РНИМУ им. Н.И. Пирогова» Минздрава России (Пироговский Университет), Москва, Россия
[2] — Акционерное общество «Группа Компаний МЕДСИ», Москва, Россия
[3] — ГБУЗ «ГКБ № 31 имени академика Г.М. Савельевой ДЗМ», Москва, Россия

ЛЕГКОЕ ТЕЧЕНИЕ ГЕМОРРАГИЧЕСКОЙ ЛИХОРАДКИ С ПОЧЕЧНЫМ СИНДРОМОМ У ПАЦИЕНТКИ СО СПОНДИЛОАРТРИТОМ, АССОЦИИРОВАННЫМ С HLA-B27

S.N. Marshala[1,2], M.D. Iarovoi [1], T.Ya. Chernobrovkina[1], I.V. Semenyakin[2], E.V. Reznik[1,2,3]

[1] — Pirogov Russian National Research Medical University, Moscow, Russia
[2] — «Medsi group» Joint Stock Company, Moscow, Russia
[3] — City Clinical Hospital № 31 n.a. G.M. Savelieva of the Moscow Health Department, Moscow, Russia

Mild Course of Hemorrhagic Fever with Renal Syndrome in A Patient with HLA-B27 Positive-Spondylarthritis

Резюме

Геморрагическая лихорадка с почечным синдромом (ГЛПС) — острое инфекционное заболевание вирусной этиологии, главным осложнением которого является тяжелое поражение почек. Для заболевания характерно цикличное течение, выделяют 4 периода (лихорадочный, олигурический, полиурический, реконвалесценция). На территории России заболевание встречается практически повсеместно, однако эндемичными районами является Дальний Восток, Урал, Поволжье. В патогенезе заболевания наибольшее значение имеет развитие поражения эндотелия сосудов, где происходит репродукция вируса, что ведет к повышению проницаемости сосудистой стенки с развитием геморрагического синдрома, отеков. Кроме того, кровоизлияниям способствует снижение факторов коагуляции, а также тромбоцитов. В литературе описаны случаи легкого течения этого заболевания у пациентов-носителей аллеля human leukocyte antigen (HLA)-B27. Целью нашей статьи является демонстрация клинического случая легкого течения ГЛПС у пациентки со спондилоартритом, ассоциированным с HLA-B27. Пациентка имела длительный субфебрилитет, а также лимфаденопатию пахового лимфоузла. Заболевание протекало без поражения почек, развития геморрагического синдрома, которые являются характерными проявлениями ГЛПС. Выявленные IgG и IgM к хантавирусам (возбудителям ГЛПС) подтвердили диагноз. Пациентка имела спондилоартрит, ассоциированный с HLA-B27, наличие которого, по данным литературы, может сделать клиническую картину менее яркой, что и наблюдается в нашем случае. В результате патогенетического лечения глюкокортикоидами достигнут регресс жалоб и улучшение состояния пациентки. Данная статья будет полезна специалистам разных профилей, так как клиническая картина ГЛПС имеет множество неспецифических симптомов, которые могут быть расценены, как проявления различных заболеваний.

Ключевые слова: *геморрагическая лихорадка с почечным синдромом; спондилоартрит; HLA-B27; хантавирус*

Конфликт интересов

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Abstract

Hemorrhagic fever with renal syndrome (HFRS) is an acute infectious disease of viral etiology, the main complication of which is severe kidney damage. The disease is characterized by a cyclic course, there are 4 periods (febrile, oliguric, polyuric, recollection). In Russia, the disease occurs almost everywhere, but endemic areas are the Far East, the Urals, and the Volga region. In the pathogenesis of the disease, the greatest significance is the development of vascular endothelial damage, where virus reproduction occurs, leading to increased permeability of the vascular wall with the development of hemorrhagic syndrome, edema. In addition, hemorrhages are promoted by a decrease in coagulation factors, as well as platelets. Cases of mild course of this disease in patients carrying the human leukocyte antigen (HLA)-B27 allele have been described in the literature. The aim of our article is to demonstrate a clinical case of mild course of HFRS in a patient with spondyloarthritis associated with HLA-B27. The patient presented with prolonged subfebrileitis as well as inguinal lymphadenopathy. The disease proceeded without kidney damage, development of hemorrhagic syndrome, which are characteristic manifestations of HFRS. Detected IgG and IgM to hantaviruses (causative agents of HFRS) confirmed the diagnosis. The patient had spondyloarthritis associated with HLA-B27, which, according to the literature, can make the clinical picture less vivid, which is observed in our case. Pathogenetic treatment with glucocorticoids resulted in regression of complaints and improvement of the patient's condition. This article will be useful for specialists of different profiles, as the clinical picture of HFRS has many nonspecific symptoms that can be considered as manifestations of various diseases.

Key words: *hemorrhagic fever with renal syndrome; spondyloarthritis; HLA-B27; hantavirus*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Mild course of hemorrhagic fever with renal syndrome in a patient with HLA-B27 positive-spondylarthritis» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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HFRS — hemorrhagic fever with renal syndrome, CCL — chemokine C-C ligands, CXCL — chemokine (C-X-C motif) ligand, CRP — C-reactive protein, HLA — human leukocyte antigen, DIC — disseminated intravascular coagulation, RNA — ribonucleic acid, PCR — polymerase chain reaction, US — ultrasound, NSAIDs — non-steroid anti-inflammatory drugs

Introduction

Hemorrhagic fever with renal syndrome (HFRS) is an acute zoonotic viral disease transmitted aerogenically (~80 %) via the air-dust route, mostly affecting small vessels and manifesting as hemorrhagic syndrome, hemodynamic disorders, specific kidney injury [1].

The disease is caused by viruses from the *Hantaviridae* family, *Orthohantavirus* genus (in the prior classification they belonged to the *Bunyaviridae* family and *Hantavirus* genus). Over 80 serotypes have been described for these viruses, with 25 of those being pathogenic for humans. The following types are most prevalent in the Russian Federation: *Puumala* (PUUV), *Seoul* (SEOV), *Amur* (AMRV), *Hantaan* (HTNV), *Dobrava* (DOBV), *Tula* (TULV), *Topograf* serotype detected in Taimyr, and *Khabarovsk* hantavirus described in the Russian Far East [2].

Russia is the second country by HFRS prevalence (~6,000 cases annually) after China (~50,000 cases annually). Endemic Russian regions include the Urals, Ulyanovsk, Samara, Orenburg Regions, Khabarovsk Krai. 85 % of all HFRS cases in Russia are reported in Povolzhie [3].

About 85 % of patients with HFRS are 25–45 years old, i.e. they belong to the able-bodied population. Humans are not epidemiologically hazardous.

The duration of the incubation period is 1 to 4 weeks.

4 consecutive periods are described in the disease course [4, 5]:

- Feverish (initial) period, lasting 3 to 7 days, is manifested by the flu-like syndrome (myalgia, facial and neck hyperemia, fever, low back pain, dyspepsia, with possible hemorrhagic signs). According to some data, visual disorders may be observed («flies in eyes», myopia, etc.);
- Oliguric period lasts 6 to 12 days and is characterized by diminished fever, worsening patient condition due to emerging renal failure, worsening

hemodynamic disorders, hemorrhagic syndrome (of the vasculitic-purpuric type); it is often accompanied by low back pain, abdominal pain, nausea, vomiting;
- Polyuric (diuretic) period in average lasts 6–14 days and is mainly accompanied by increased diuresis (~3–10 L/day), nocturia, thirst; hypokalemia may lead to muscular weakness, paralytic ileus, tachycardia (arrhythmias);
- Reconvalescence stage (early — within 2 months; late — within 2 years) is characterized by asthenic and autonomous-vascular syndromes, development of persistent immunity, recovery of hemostasis and renal function with the possible emergence of tubular failure.

The primary viral reproduction occurs in epitheliocytes of the upper respiratory tract even before the first clinical signs of the disease emerge. The next viral target is endothelial cells, in particular those of the blood-lung barrier, with ~~subsequent~~ viremia [6].

Endotheliocyte injury specifically plays a main role in the pathogenesis of HFRS — it leads to enhanced permeability of the vascular wall with subsequent edema and hemorrhages. Another pathogenetic event is the impaired coagulation, with confirmed decreased expression of von Willebrand factor and thrombospondin-1 (a substance destroying von Willebrand factor and causing fibrin degradation) by infected endothelial cells. This leads to thrombocytopenia, a pathognomonic laboratory parameter in HFRS [7–10].

On the other hand, a large amount of biologically active substances is released, including chemokines CCL4 (chemokine C-C ligand 4), CCL5, CXCL9 (chemokine (C-X-C motif) ligand 9), CXCL10, and CXCL12 that enable the migration of white blood cells via the vascular wall. CCL2 and CCL5 provide the chemotaxis of monocytes and T-helpers type 1, natural killer (NK)-cells and T-cytotoxic lymphocytes. T-cytotoxic lymphocytes play a specifically defining role in the antiviral protection against Orthohantaviruses [6].

Table 1. *Complications of HFRS (cited in [5]).*

Acute complications	Chronic complications
1. Arterial hypertension 2. Electrolyte disturbances 3. Infectious-toxic shock 4. Hemorrhage and necrosis of the pituitary gland 5. Meningoencephalitis 6. Acute kidney injury 7. Pulmonary edema. 8. Pericarditis. 9. Myocarditis. 10. Disseminated intravascular coagulation (DIC). 11. Gastrointestinal bleeding	1. Arterial hypertension 2. Hypopituitarism 3. Hypothyroidism 4. Chronic tubulointerstitial nephritis with tubular proteinuria 5. Chronic membranoproliferative glomerulonephritis

The literature describes features of the immune response in HFRS associated with the major histocompatibility complex (HLA) and immunological reactivity (IR) genes affecting the predisposition to the disease and HFRS severity (features).

Epidemiological (dwelling in the HFRS spots, possible contact with animal carriers), clinical, and laboratory data are used in the HFRS diagnosis. The laboratory diagnosis includes the following alterations in the complete blood count and the biochemistry panel: leukopenia transforming to leukocytosis; thrombocytopenia directly correlating with the disease severity. Creatinine, C-reactive protein (CRP) levels also increase, while C3 complement levels drop. Besides, high procalcitonin, interferon γ, tumor necrosis factor α, and interleukin 10 levels are also observed. Interleukin 6 levels in the blood serum and urine also increase. Serological diagnosis is based on detecting IgM and IgG antibodies against hantavirus using the enzyme-linked immunosorbent assay. Besides, polymerase chain reaction (PCR) is used to detect the ribonucleic acid (RNA) of the virus in biological fluids (blood) [11–14]. The infection leaves a lifelong type-specific immunity.

Complications after the HFRS may be divided into acute and chronic (Table 1).

Ethiotropic HFRS therapy includes ribavirin — a drug suppressing the synthesis of viral RNA and protein. However, its use is efficient only in the early stage (first 4 days) [15].

The article presents a description of a mild HFRS case without kidney injury, but with atypical clinical signs.

Clinical case study

A 41-year-old patient attended the physician in August 2024 complaining of pain in the left inguinal region, most significant with walking, worsening with the hip flexion and adduction; pain in the pubic region, daily fevers up to 39 °C, voice hoarseness, dry non-intensive cough. During interrogation, she noted pain in the lumbar spine, with the morning stiffness up to 60 minutes, irradiation to the left thigh along its posterolateral surface up to the upper third, especially when standing up. The patient had this symptom for 2 years.

History: 7 days before the visit she developed fever (~39 °C) for several days, general weakness, dizziness; 3 days later she developed pain in the left inguinal region. To relieve fever, she took paracetamol in the dose of 500 mg up to 3 times daily for 5 days. Since the emergence of fever, her lumbar pain and hip pain (mostly left-sided) got worse; she also developed pain in small hand joints. It was confirmed that in February 2024 the patient traveled to the Irkutsk Region, in March 2024 — to Povolzhie (Samara) and Kaliningrad, in April 2024 — to Sochi, in May 2024 — to Rostov-on–Don and Turkey.

She denied contacts with animals, animal, insect, or arthropod bites during the preceding month.

On physical examination, the patient's condition was satisfactory; the skin was clean, had normal color and moisture level; visible mucous membranes were normal, no edema was detected. She had no catarrhal events. The tongue was coated with white plaque; tonsils were not enlarged. Body temperature: 36.6 °C. Visible lymph nodes were non-tender on palpation, not enlarged, but mobile. The pubic symphysis was tender on palpation. Vesicular breathing with no rales was auscultated in lungs. The respiratory rate was 16/min, with SpO_2 98 %. Cardiac tones were clear, regular, with no murmurs; the pulse rate was 70 beats per minute, blood pressure was 130/70 mm Hg in both arms. The abdomen was soft, non-tender; peritoneal irritation signs were negative. The liver and spleen were not palpable; they were not tender. Costovertebral tenderness was negative bilaterally. Positive straight leg raise was reported for the left lower extremity.

The patient constantly took Norethisterone from July till August 2024 as per the gynecologist recommendation.

Investigations: IgM-antibodies against herpes simplex viruses 1 and 2 0.45 (hereinafter reference ranges are given in parentheses; 0–0.8 of the cutoff index (COI)). IgM-antibodies against the Varicella Zoster virus 0.33 (0–0.79) COI; superficial antigen of the hepatitis B virus (HBsAg) not detected; total antibodies against the hepatitis C virus were not detected. Antibodies against the human immunodeficiency viruses 1 and 2 were not detected.

PCR screening for RNA of Influenza virus A, Influenza virus B, Influenza virus A/H1N1, RNA of human Respiratory Syncytial virus (hRSv), metapneumovirus was negative.

Antinuclear factor (HEp-2 cell line), antibodies against the double-stranded (native) DNA (anti-dsDNA), various antinuclear antibodies (anti-Sm, RNP, SS-A, SS-B, Scl-70, PM-Scl, PCNA, dsDNA, CENT-B, Jo-1, anti-histone, anti-nucleosome, Ribo P, AMA-M2) were all within reference ranges.

The genetic test (PCR) revealed the HLA-B27 gene.

Changes in blood parameters are presented in Table 2.

The urinalysis demonstrated a small amount of mucus, otherwise without clinically significant deviations.

After the primary visit, Lornoxicam (8 mg twice daily) was started; it continued for 14 days along with the examination.

Electrocardiography: sinus rhythm, heart rate 67 beats per minute, normal electrical axis, non-specific ST-segment changes.

Ultrasound (US) of lymph nodes revealed signs of lymphadenopathy of axillary and ilioinguinal regions, suggesting lymphadenitis (sized from 13x9 mm to 22x11 mm). A large irregularly shaped lymph node sized 26x18 mm was detected in the left inguinal fold, with significant hilar and perifocal blood flow (signs of severe left-sided inguinal lymphadenitis with hypervascularization and reactive lymphangitis).

Abdominal US demonstrated moderate hepatosplenomegaly, thickened gallbladder walls, and diffuse changes in the pancreatic parenchyma.

Magnetic resonance imaging did not reveal any signs of sacroiliitis, coxitis, synovitis of hip joints. Pubic symphysitis, signs of myositis in the left adductor longus, pectineus, obturator externus, and adductor brevis muscles were detected.

Due to the prolonged disease course and epidemiological history, hemorrhagic fever with renal syndrome was suspected. IgG — 0.3 (< 0.8) COI and IgM — 3.2 (< 0.8) COI against hantaviruses (causative agent of HFRS) were detected in blood. Yersiniosis and pseudotuberculosis were excluded. The following diagnosis was established: Mild hemorrhagic fever with renal syndrome (positive IgM-antibodies against hantaviruses). Spondyloarthritis: inflammatory back pain, symphysitis, peripheral arthritis (2nd metacarpophalangeal joint), right-sided coxitis, high activity.

Table 2. *Dynamics of the patient's blood parameters*

Analysis, units of measurement	05.08.	09.08.	19.08.	26.08.	29.08.	06.09	11.09	25.09	Reference values
C-reactive protein, mg/l	122	61,37	36	31,6	21,86	15,64	13,65	4,26	0-5
Erythrocyte sedimentation rate, mm/hour	61	76	36		83	66	69	25	0-20
Aspartate amino transferase, U/L		62,8							<35
Creatinine, μmol/L		63				58			58-96
Glomerular filtration rate CKD-EPI, мл/мин/1,73 м^2		106				110			88-128
Leukocytes, 10^9/л		11,08	10,98	10,34	8,58	9,45	7,47	12,2	4,5-11
Neutrophils, %		72,5	64,8	71,9	64,5	63,2	59,8	68,1	47-72
Platelets, 10^9/л		460	505	433	419	406	423	341	150-400

Note: CKD-EPI — chronic kidney disease epidemiology collaboration

5 days later, the patient had no effect from non-steroid anti-inflammatory drugs (NSAIDs), while she developed swelling of the left labium major, 6-day delay in the menstrual cycle, and an episode of fever (max. 37.3 °C). Therapy was adjusted — Prednisolone 30 mg (with dose tapering by 10 mg every 2 days) was added as anti-inflammatory treatment. Due to prolonged HFRS course, it was decided to abstain from ribavirin therapy.

Further outpatient examination (US) revealed signs of symphisitis, tendinitis of the rectus abdominis muscle, swelling of the subcutaneous fat in the pubic region and the left labium major, reactive changes in inguinal lymph nodes.

The patient was also administered Esomeprazole (20 mg), Calcium carbonate + Cholecalciferol (500 mg + 400 IU twice daily). After the treatment adjustment, the patient's symptoms improved — the labium major swelling regressed, although tenderness persisted with the flexion of the second digit in the right hand, as well as pain and swelling in the pubic symphysis region.

Within a month, clinical symptoms improved more — pain in the inguinal region regressed, the lymph node shrunk in size, and the body temperature normalized. Current data about the patient condition are not available due to her transfer to another medical institution.

Discussion

Based on the history (visiting regions with epidemiological HFRS prevalence), clinical signs (fever, hepatomegaly), laboratory tests (specific IgM-antibodies against hantaviruses), HFRS was suspected. This patient had atypical HFRS course: the fever stage was not significantly severe — only episodes of fever were reported without other clinical signs. The course did not correspond to classic periods (hypertension, oliguria with subsequent polyuria were missing).

The patient had a history of spondyloarthritis manifesting with pain in the lumbar spine for 2 years. It has been established that spondyloarthritis is associated with the HLA-B27 gene allele [16].

HLA-B27 gene is one of the most common B alleles in the European population. The prevalence of this gene among the United States population is 0.6–1 %. This major histocompatibility complex variant provides the presentation of antigens with cytotoxic T-lymphocytes $CD8^+$ (Cluster of Differentiation 8) (CTL), enabling the antiviral immune response, and with NK-cells [17].

Besides, HLA-B27 gene defines the patient predisposition to rheumatological diseases, in particular spondyloarthritis (Table 3).

HLA-B27 allele is associated not only with the aforementioned rheumatic diseases, but also with a mild HFRS course (no acute kidney injury, thrombocytopenia, significant hemorrhagic syndrome) [18]. Korva M. et al. associate it with the antiviral role of this gene [19].

Such observations were described by Mustonen J. et al., which demonstrated a quicker recovery of patients with HFRS, rare kidney injury, and less significant leukocytosis. Besides, authors confirm that less severe course of the human immunodeficiency virus-infection is also observed in patients with the HLA-B27 allele [20]. Similar results were also observed in our patient who had a combination of HLA-B27 and mild HFRS without kidney injury and typical disease course. Besides, the patient's condition improved even without specific ethiotropic therapy, which is also typical for HFRS in patients with HLA-B27.

Conclusion

Thus, the HLA-B27 carrier state may significantly alter clinical signs of HFRS, which proves the importance of interdisciplinary approach in the diagnosis and treatment of this disease. Thus, patients, with a burdened epidemiological history, prolonged fever, and kidney injury should be considered as those in the risk group for HFRS.

Table 3. *HLA-B27 associated diseases (cited from [17])*

Name of disease	Clinical features	Frequency of occurrence of HLA-B27 gene in this pathology, %
Ankylosing spondylitis	Lesions of the sacroiliac joints and joints of the spine	94
Reactive arthritis	Non-septic arthritis of large joints due to GI or genitourinary infections	30-75
Spondyloarthritis associated with colitis	Lesions of the sacroiliac and spinal joints and other large joints in patients with Crohn's disease and nonspecific ulcerative colitis	33-75
Psoriatic spondyloarthritis	Lesions of the sacroiliac and spinal joints and other large joints in patients with cutaneous psoriasis	40-50
Arthritis associated with juvenile enthesitis	Arthritis of large joints in adolescent patients	76
Acute anterior uveitis	Nonseptic lesion of the anterior chamber of the eye	50

Вклад авторов:

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Маршала С.Н.: подбор клинического случая, подбор и обработка визуального материала, редактирование текста

Яровой М.Д.: написание статьи, анализ клинического случая, обзор литературы, перевод на английский язык

Чернобровкина Т.Я.: анализ клинического случая, редактирование рукописи

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Author Contribution:

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

Marshala S.N.: case study selection, selection and processing of the visual materials, text editing

Iarovoi M.D.: article writing, literature review, case study analysis, translation into English

Chernobrovkina T.Ya.: clinical case analysis, manuscript editing

Semeniakin I.V.: text editing Reznik E.V.: article writing, text editing

Reznik E.V. — idea, leadership, work organization, edition

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Информация об авторах

Маршала Сергей Николаевич — руководитель центра персонифицированной Медицины МЕДСИ на Мичуринском проспекте, врач-терапевт, ревматолог, ассистент кафедры пропедевтики внутренних болезней № 2 Института клинической медицины ФГАОУ ВО РНИМУ им. Н.И. Пирогова МЗ России (Пироговский Университет), Москва, email: marshala_2011@mail.ru, ORCID ID: https://orcid.org/0009-0004-9738-7447)

Яровой Максим Дмитриевич ✉ — студент 5 курса лечебного факультета ФГАОУ ВО РНИМУ им. Н.И. Пирогова МЗ России (Пироговский Университет), Москва, email: jarovojmax@mail.ru, ORCID ID: https://orcid.org/0009-0008-4580-8851)

Чернобровкина Татьяна Яковлевна — к.м.н., врач высшей категории, доцент кафедры инфекционных болезней и эпидемиологии Института клинической медицины ФГАОУ ВО РНИМУ им. Н.И. Пирогова МЗ России (Пироговский Университет), врач ультразвуковой диагностики, Москва, email: tychernobr@gmail.com ORCID ID: https://orcid.org/009-0008-3853-4792

Семенякин Игорь Владимирович — д.м.н., профессор, медицинский директор АО «Группа компаний «МЕДСИ», Москва, e-mail: semeniakin.iv@medsigroup.ru, ORCID ID: https://orcid.org/0000-0003-3246-7337

Резник Елена Владимировна — д.м.н., доцент, заведующий кафедрой пропедевтики внутренних болезней № 2 Института клинической медицины, ФГАОУ ВО «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» МЗ РФ (Пироговский университет), Москва; врач-терапевт, кардиолог, врач функциональной диагностики, ультразвуковой диагностики, клинический фармаколог, ГБУЗ «ГКБ № 31 им. Г.М. Савельевой ДЗМ», Москва, e-mail: elenaresnik@gmail.com, ORCID ID: http://orcid.org/0000-0001-7479-418X

Information about the authors

Sergey N. Marshala — MD, Head of the «Medsi group» Joint Stock Company, Center for Personalized Medicine on Michurinsky Prospekt, internist, rheumatologist, assistant of the Department of Propaedeutics of Internal Diseases № 2 of the Institute of Clinical Medicine of the Pirogov Russian National Research Medical University, Moscow, Russia, email: marshala_2011@mail.ru, ORCID ID: https://orcid.org/0009-0004-9738-7447

Maksim D. Iarovoi ✉ — a 5th year student of the Federal State Autonomous Educational Institution of Higher Education the Pirogov Russian National Research Medical University, Moscow, email: jarovojmax@mail.ru, ORCID ID: https://orcid.org/0009-0008-4580-8851

Tatiana Ya. Chernobrovkina — cms, Associate Professor of the department of infectious diseases and epidemiology of the Institute of Clinical Medicine of the Russian National Research Medical University named after N.I. Pirogov of the Ministry of healthcare of the Russian Federation, Moscow, email: tychernobr@gmail.com/ ORCID ID: https://orcid.org/009-0008-3853-4792

Igor V. Semeniakin — MD, PhD, professor, Medical Director of the "Medsi group" Joint Stock Company, e-mail: semeniakin.iv@medsigroup.ru, ORCID ID: https://orcid.org/0000-0003-3246-7337

Reznik Elena Vladimirovna — MD, PhD, Head of the Department of Internal disease Propedeutics № 2 of Institute of Clinical Medicine of the Russian national research medical University named after N.I. Pirogov of the Ministry of healthcare of the Russian Federation, Moscow; Cardiologist of the GBUZ № 31 named after academician G.M. Savelieva of Healthcare Department of Moscow, Moscow, e-mail: elenaresnik@gmail.com, ORCID ID http://orcid.org/0000-0001-7479-418X

✉ Автор, ответственный за переписку / Corresponding author