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THE MAIN CLINICAL SYNDROMES ASSOCIATED WITH ACTIVE CRONIC ATIPICAL EPSTEINE-BARR VIRUS INFECTION: CREATED ALGORITHM OF CLINICAL AND LABORATORY DIAGNOSTIC

I.V. Nesterova[1,3], E.O. Khalturina[2,3]

[1]Kuban State Medical University, Krasnodar, Russia
[2]I.M. Sechenov First Moscow State Medical University, Moscow (Sechenov University), Moscow, Russia
[3]Clinical and diagnostic center MEDSI on Belorusskaya, Moscow, Russia

Abstract. The annual steady increase of the herpesviral infections number in the human population is one of the most important interdisciplinary problems of modern medicine. Clinicians and laboratory diagnostics physicians face difficulties in clinical symptoms assessing, inadequate laboratory diagnostics and difficulties in interpretation of the obtained results. This is connected with a low awareness of atypical chronic active infection symptoms caused in particular by the Epstein-Barr virus (EBV), of the ability to fully diagnose, and of serious consequencescaused by prolonged activity of herpesviruses in the human body. Studies were carried out to determinethe functioning features of the antiviral defense system, as well as defects and disorders in the interferon system in patients suffering from various mono-, mixed herpesvirus infections and bacterial co-infections. The main clinical syndromes associated with these herpetic infections, as well as prevailing nosological forms of concomitant diseases, have been identified. Among the group of patients suffering from mono-herpesvirus infections, the leading position takes the allergic syndrome (55%), while the syndrome of chronic fatigue syndrome (85%) and the infectious syndrome (68%) prevail in the incidence of patients with mixed herpesvirus infections. Extended testing of the antiviral protection main mechanisms state made it possible to identify the most frequent defects in the functioning of antiviral immunity: disturbances in induced production of IFNα and IFNγ, deficiency of cytotoxic T lymphocytes, deficiency of natural killer cells, including EKT, and / or inadequate absence of their activation, neutropenia. The revealed clinical syndromes and functioning features of the antiviral defense system will allow us to further develop the concept of complex, individualized, etio- and immunopathogenetic therapy.

Key words: herpesvirus infection, antiviral defense, interferon

Corresponding author: Irina Vadimovna Nesterova, Doctor of Medical Science, Professor — Professor of Allergology and Immunology, Peoples' Friendship University of Russia, Moscow, Russia, Ministry of Health of the Russian Federation, 117198, Moscow, Miklukho-Maklaya str., 6.
E-mail: inesterova1@yandex.ru

Nesterova I.V. SPIN: 4714-2488, ORCID: 0000-0002-5339-4504
Khalturina E.O. SPIN: 2813-4952; ORCID: 0000-0002-8948-8983

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In recent years, herpetic infections have occupied a special position in the infectious diseases structure. These infections are characterized by a high prevalence, high virus carrying incidence, atypical course and a diverse clinical picture, as well as the complexities of clinical and laboratory diagnostics. The herpetic infections occur in the form of mono, mixed and co-infections and can be asymptomatic (latent), in acute, chronic persistent form with recurrent course, and also in the form of atypical chronic active infection (AChA).

Herpesvirus infections are a group of human infectious diseases caused by viruses of the Herpesviridae family. Nowadays this family includes 8 types of herpesviruses. Phylogenetically, these viruses belong to the subfamilies: Alphaherpesvirinae — herpes simplex virus (HSV) type 3 and varicella-zoster virus (Varicella Zoster Virus); to Betaherpesvirinae — cytomegalovirus (CMV), human herpesvirus (HHV) of type 6 A and B, HSV of type 7; to Gammaherpesvirinae-Epstein-Barr virus (EBV), HSV of type 8 (Kaposi's sarcoma virus) [1, 2]. Viruses of this family have many similar mechanisms and ways of transmission, which causes their wide distribution in the human population. Infection of children occurs in early childhood because of a developing immune system, which determines the specific features of the course of these infections, the high incidence of mixed herpesviral infections and co-infections of bacterial and viral etiology, and creates conditions for a lifelong persistence of viruses and the formation of a virus carriage [3—5].

Of particular interest among the viruses of this family is EBV (HSV of type 4), which is most often the causative agent of AChA in both mono and mixed infections. It has a tropism for the nervous and epithelial cells and, in addition, they infect cells of the immune system — the cells of the thymus, monocytes / macrophages, neutrophils, B-lymphocytes, and are found in T-lymphocytes. The peculiarity of EBV is its ability to cause not only cytolysis, but also the proliferation of infected B-lymphocytes [6, 7]. It has an affinity for the CD21 receptor of B-lymphocytes, which contributes to its specific binding to it and penetration into the cell, where it is actively reproduced, exploiting the various mechanisms of the cell itself [8—10].

One of the main features of herpesviruses is a lifelong persistence of the pathogen in the human body. In this case, the further fate of the virus, as well as the presence or absence of clinical manifestations of the disease depends on how well the antiviral mechanisms of the immune system and the interferon system function [11—13].

The main problem that arises in facing of the human body with various herpesviral infections, and especially with EBV, is the presence of defects in the interferon system and immune system disorders by the type of immune deficiency (ID) that can be both congenital, genetically conditioned, and secondary — acquired character [15—17]. When there are defects in the IFN system and / or ID, as a rule, serious nosological forms of diseases caused by herpesviruses develop, which flow extremely hard, often with the development of systemic complications leading to disability of the patient [18—20].

The main clinical features of mixed herpetic infection are: prolonged feeling of severe weakness, chronic fatigue, patients are concerned about sweatiness, unstable pain in the throat, in muscles and joints, headaches, low-grade fever, lymphadenopathy, sleep disturbance, decrease in memory, concentrating, mental impairment, less often — psychogenic depression. Often there are virus-associated repeated ARVI, chronic recurrent herpes-viral infections (HSV1, HSV2), chronic CMV and HHV6 infections, chronic bacterial and fungal infections.

The purpose: to structure the algorithm of the complex clinical and immunological study, which allows to identify the variants of antiviral protection immune mechanisms disorders; to reveal the features of clinical syndromes associated with immunodeficiency, in mono- and mixed-herpes-viral infections.

MATERIALS AND METHODS

We have observed 198 patients aged between 23 and 60 years old, suffering from mono and mixed herpes virus infection.The study was carried on Clini-

cal and diagnostic center MEDSI on Belorusskaya. The study was approved by the Ethics Commission, all patients have given an informed consent to participate in the study in accordance with WMA Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, 2013) and the processing of personal data.

Combined with the traditional methods (collection of anamnesis, methods of physical examination, CBC, etc.) for the detection of herpesviral infections, serological tests were used (IgM VCA EBV, IgG VCA EBV, IgM CMV, IgG CMV IgM HSV1 / 2, IgG HSV1 / 2) using the ELISA test systems of the "Diagnostic Systems" SPA (Russia), as well as the PCR test system "AmpliSens" (Russia) to detect the genome of viruses in biomaterials (blood, saliva, urine, scraping from the tonsils and the posterior pharyngeal wall). To evaluate the features of the functioning of antiviral immunity (immunogram, INF-status, etc.), flow cytometry and ELISA methods were used.Statistical analysis was performed using the Microsoft Excel 2010 software package.

RESULTS OF THE STUDY AND DISCUSSION

We determined the incidence of mono- and herpesvirus infections in the observed group of patients.

According to the obtained data, 36.6% of patients suffer from mono-herpesvirus infections, 55.5% of them are patients with EBV; 35.3% with HSV of type 1 and 11.1% with HSV of type 2 and CMV, respectively.

EBV (35.4%), CMV (22.5%) and HSV of type 1 (19.3%). occupy the dominant position in the etiology of mono-infections (Fig. 1) 63.7% of the patients were infected by mixed herpesvirus infections.

The dominating combinations in the structure of these infections are HSV1 + HSV2; EBV + HHV of type 6, EBV + CMV + HHV 6 (11.2%), EBV + + CMV + HHV 6 + HSV 1 — 11.2% each. Further, the distribution of mixed infections by the occurrence of combinations is as follows: EBV + CMV (9.7%); EBV + CMV + HSV1 (4.8%); VEB + CMV + + HSV2 (3.2%), EBV + HHV 6 (11.2%) (Fig. 2).

In the course of the study, a number of clinical features characteristic of AChA mixed herpes infection were identified, which included a prolonged feeling of severe weakness, chronic fatigue, beyond that the patients complain of sweating, unstable pain in the throat, muscles and joints, headaches, low-grade fever, lymphadenopathy, sleep disturbance, decrease in memory, concentrating, mental impairment, less often — psychogenic depression. Often there are virus-associated repeated ARVI, chronic recurrent herpes-viral infections (HSV1, HSV2), chronic CMV and HHV 6 infections, chronic bacterial and fungal infections. Associated with AChA diseases are characterized by a recurrent course.

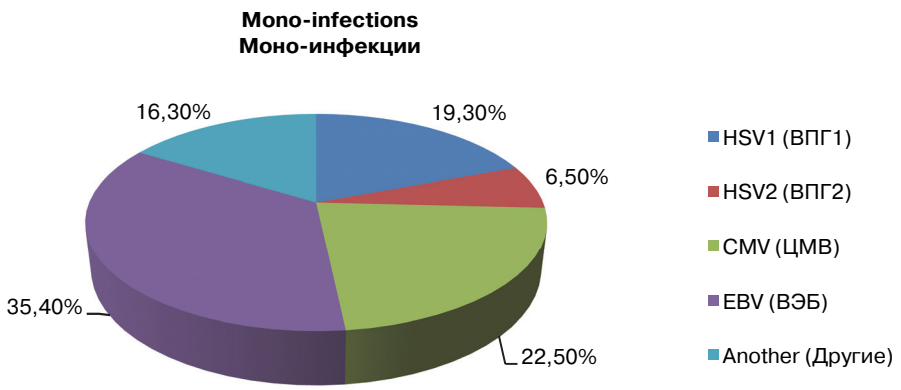

Fig. 1. The etiological structure of mono-herpesvirus infections

Рис. 1. Этиологическая структура моно герпесвирусных инфекций

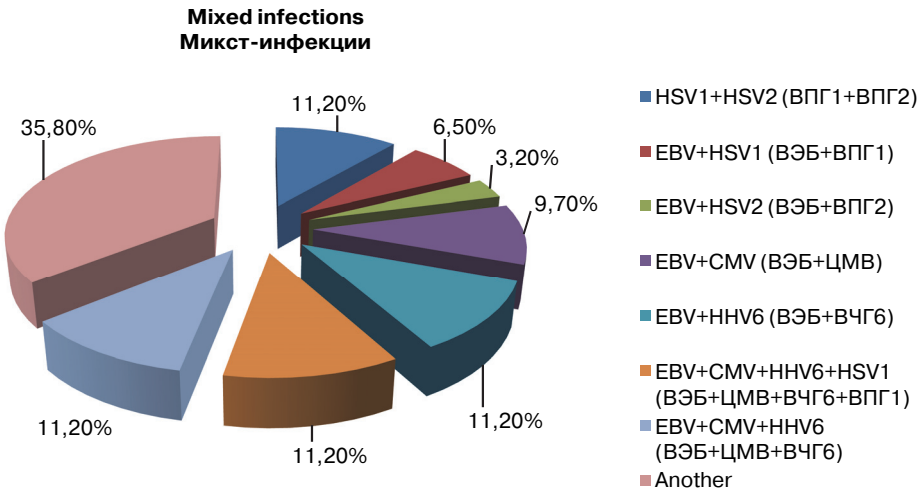

Fig. 2. The etiological structure of mixed herpesvirus infections

Рис. 2. Этиологическая структура микст герпесвирусных инфекций

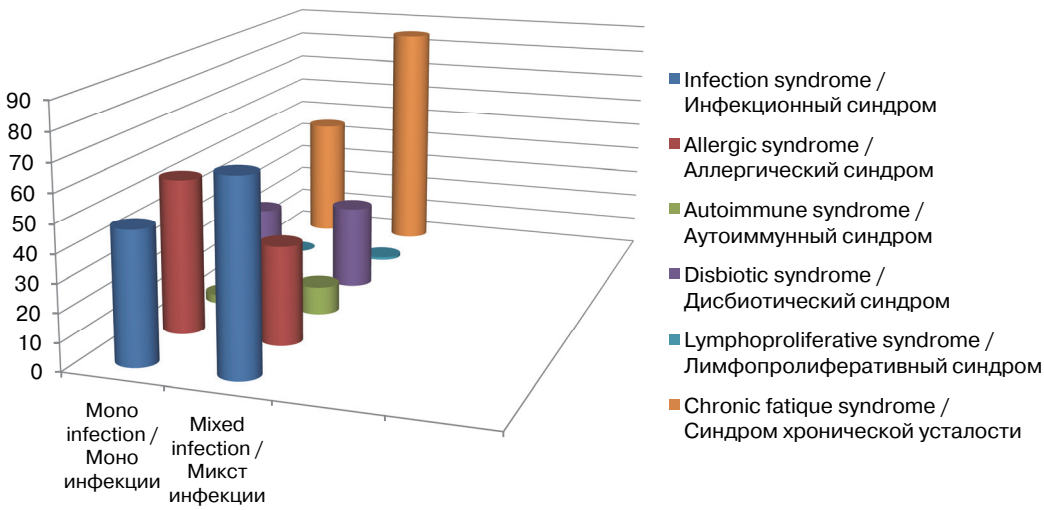

Fig. 3. The main clinical syndromes associated with herpesvirus infections

Рис. 3. Основные клинические синдромы, ассоциированные с герпесвирусной инфекцией

Analysis of the existing concomitant diseases and conditions in patients suffering from mono and mixed herpetic infections made it possible to identify the 5 main syndromes that occur most frequently. These syndromes include: chronic fatigue syndrome (CFS), infectious, allergic, autoimmune and dysbiotic syndrome.

Among the group of patients suffering from mono-herpesvirus infections, the leading position is in the allergic syndrome (55%), while the chronic fatigue syndrome (85%) andthe infectious syndrome (68%) prevail in the incidence of patients with mixed herpesvirus infections.

At present, the role of viral infection as an etiologic factor in the development of CFS is considered proven in medicine. CFS often has a variety of clinical manifestations. Patients are concerned about:

- Long term low grade fever;
- Throat pain and discomfort;
- Increased sweatiness, sensitivity to cold;

- Headache, migraine;
- regional lymphadenopathy;
- neurological disorders (paresthesia, synaesthesia, sensitivity disorders, low muscle tone, etc.);
- increased fatigue, a significant decrease in efficiency;
- decrease in memory processes, difficulty concentrating;
- headaches, joint pain, myalgia;
- increasedfatigue, inadequatephysicalorpsychoemotional stress;
- sleep disorders (insomnia or increased drowsiness);
- panic attacks, mood disorders; emotional lability; psychogenic depression etc;
- brittleness of nails, hair loss.

The obtained data indicate that in all patients suffering from CFS associated with mono- or mixed herpes-viral infections, in 100% of cases there are various mono- or combined defects in the immune system functioning — immunodeficiency, rarely congenital, but more often acquired character, including various disorders of the interferon system. These disorders are associated with clinical syndromes, which, as a rule, accompany immunodeficiency.

In the structure of the infectious syndrome among the etiological factors, bacterial and viral co-infections are most often observed. Localization of the infectious inflammatory process may be different, but in the predominant majority of cases, the organs of the upper and lower respiratory tract (tonsillitis, pharyngitis, sinusitis, bronchitis, etc.), skin and its appendages (pyoderma, furunculosis, etc.) are affected.

Allergic syndrome ranks second in incidence and is found in 55% of patients with mono- and 35% with mixed herpesvirus infections. The structure of allergopathology is dominated by topical manifestations from upper and lower respiratory tract (allergic rhinitis, pharyngitis, sinusitis, bronchial asthma), allergic skin diseases (atopic dermatitis, recurrent urticaria, contact dermatitis) gastrointestinal manifestations of allergy.

When analyzing the structure of the autoimmune syndrome, the leading position is taken by the autoimmune lesion of the thyroid gland — Hashimoto disease.

The syndrome of dysbiotic disorders includes disorders of the colon microbioma, which is diagnosed in mono- and mixed herpesvirus infections in 26% and 30% of cases, respectively.

Lymphoproliferative syndrome is found in 1% of cases with mixed herpesvirus infection.

When analyzing the characteristicsof the immune system and interferon system functioning in patients with herpesvirus infections, a number of disorders were revealed in the system of antiviral immunity. And the most pronounced disorders were detected in patients with mixed herpesvirus infections. The most pathognomonic among them are:

— defects in the interferon system (serum and induced INF-α and INF-γ);

— damages of natural killer cells ($CD16^+CD56^+$, $CD16^+CD56^-$) deficiency of their number and/or function (cytotoxicity);

— decrease in antibodies level of IgG class;

— defects of neutrophilic granulocytes (neutropenia);

— deficiency of T-lymphocytes — deficiency of $CD3^+CD8^+$; defects of activation$CD3^+CD8^+$;

— deficiency or inadequate response to a virus infection $CD3^+CD8^+CD25^+$ and/or $CD3^+CD8^+HLA\text{-}DR^+$.

Reduction in induced production of IFN-α and IFN-γ was present in 100% of patients and was more pronounced than with monoinfection, HSV1 or EBV (Tab. 1).

The most pronounced and combined disorders on various parts of the antiviral protection are characteristic for the association of HSV 1/2 and AChA and EBV infections.

Infringements and an imbalance in a population structure of blood lymphocytes are revealed: deficit $CD3^+CD8^+$ cells — 88,5%, NK — 80%; EKT — 72,4%.

Table 1 / Таблица 1

**Defects in the functioning of the immune system and interferon system associated with various mixed herpesvirus infections /
Дефекты функционирования иммунной системы и системы интерферонов, ассоциированные с различными вариантами микст герпевирусной инфекции**

Marker / Маркер	Frequency of defectoccurrence (%) / Частота встречаемости (%)
1. Defects in interferon production Дефекты в системе интерферона	100
1.1. Induced IFN-α Индуцированный ИНФ-α	100
1.2. Induced IFN-γ Индуцированный ИНФ-γ	100
1.3. Serum IFN-α Сывороточный ИНФ-α	22,8
1.4. Serum IFN-γ Сывороточный ИНФ-γ	19,5
2. Defects of humoral chain Дефекты гуморального звена	32,4
2.1. Deficiency of serum Ig G Дефицит сывороточного Ig G	28,3
3. Defects of cellular arm Дефекты клеточного звена	
3.1. Deficiency of B-lymphocytes Дефицит В-лимфоцитов	8,3
3.2. Deficiency of EKK Дефицит ЕКК ($CD3^-CD56^+CD16^+$; $CD56^+DR^+$)	72,4
3.3. Deficiency of T-lymphocytes Дефицит Т-лимфоцитов	
3.3.1. Deficiency of $CD3^+CD4^+$; $CD3^+CD8^+$; $CD3^+CD56^+$ Дефицит $CD3^+CD4^+$; $CD3^+CD8^+$; $CD3^+CD56^+$	88,5
3.3.2. Inadequate response to a virus infection: $CD4^+HLADR^+$, $CD8^+$HLA DR, $CD56^+$HLA DR^+; $CD8^+CD25^+$ Неадекватный ответ на вирусную инфекцию: $CD4^+HLADR^+$, $CD8^+$HLADR, $CD56^+HLADR^+$; $CD8^+CD25$	68,2
4. Defects of neutrophilic granulocytes Дефекты нейтрофильных гранулоцитов	83,3
4.1. Neutropenia Нейтропения	81,4

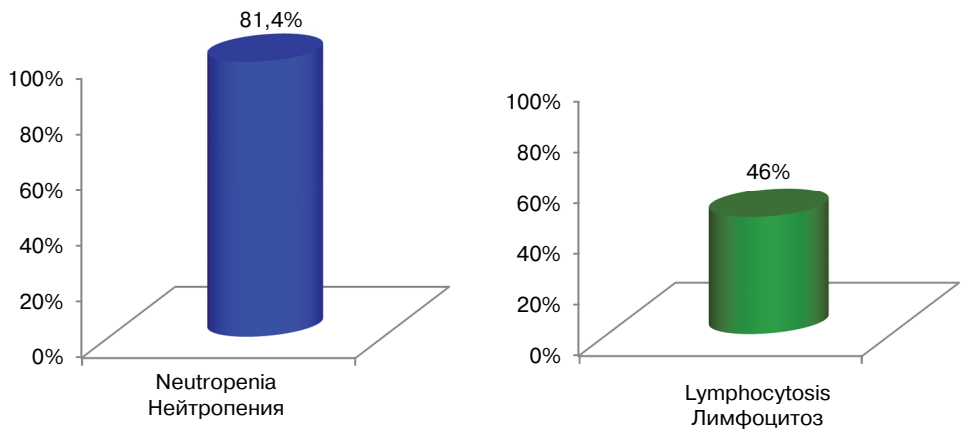

Fig. 4. Changes in occurrence of neutropenia and lymphocytosis in patients with various mixed herpesvirus infections

Рис. 4. Частота встречаемости нейтропении и лимфоцитоза у пациентов с различными микст герпесвирусными инфекциями

Table 2 / Таблица 2

Frequency of herpes virus genome detection in different biomaterials with AChA (PCR) / Частота обнаружения вирусного генома в различных биоматериалах при АХАИ (ПЦР)

Biomaterial type / Вид биоматериала	Occurrence frequency (%) / Частота обнаружения (%)
Saliva / Слюна	86,3
Blood / Кровь	8,4
Scraping from posterior pharyngeal wall / Соскоб с задней стенки глотки	72,8
Scraping from the tonsils / Соскоб с миндалин	48,7
Urine / Моча	9,3

When studying the hemograms of patients with AChA, attention is drawn to the pronounced neutropenia observed in 81,4% of cases; as well as limfocytosis (46%). In addition, cases of leukopenia and lymphocytosis are detected in 46% of patients (Fig. 4).

It has been shown that the appearance of EBNA1 expression (EBV nuclear antigen) is accompanied by the onset of lytic infection and reproduction of EBV, which again leads to its appearance in crypts of tonsils and saliva. That is why it is necessary to carry out PCR diagnostics aimed at detecting EBV in saliva, in scraping from the tonsils, in a scraping from the oropharynx. It is mandatory to quantify this virus to assess the dynamics of antiviral and immunotropic therapy. The necessity of compulsory study of these biomaterials is determined by two factors: the place of repeated reproduction of the virus and the fact that the virus circulates less frequently in the blood and a rather limited time. However, despite this, doctors most often direct the patient's blood to research.

The revealed clinical and immunological, laboratory features of AChA herpetic infections made it possible to develop a diagnostic algorithm:

1) complaints;
2) collection of immunological anamnesis;
3) clinical research;
4) instrumental diagnostics;
5) PCR diagnostics (quantitative and semiquantitative) of various biomaterials: saliva, urine, blood, scraping from tonsils and oropharynx (Table 2);
6) serodiagnosis of respiratory viral and herpesvirus infections (IgM and IgG to HSV1, HSV2, CMV, EBV (EA, EBNA, VCA), HHV6);
7) immunological research:
— interferon status (serum and induced IFN alpha and gamma) ($CD3^+CD8^+$, $CD8^+CD25^+$, $CD4^+CD8^+$, $CD16^+CD56^+$, $CD16^+CD56^-$, $CD4^+HLA\text{-}DR^+$),
— animmunogram with the determination of activation markers on cells,
— humoral chain of immunity (serum immunoglobulins Ig A, M, G),
— number and functional activity of neutrophilic granulocytes;
8) detection of autoimmunity syndrome according to clinical features;
9) detection of allergic syndrome: Ig E, ECP (eosinophilic cationic protein, specific Ig E);
10) detection mucosa microbiome of respiratory and gastrointestinal tract.

CONCLUSION

The obtained data indicate a higher incidence of mixed herpesvirus infections in the population. It has been shown that in case of mono- and mixed-herpesvirus infections, in addition to the clinical manifestations characteristic of each type of herpesvirus infection, there are various clinical syndromes characteristic of both congenital and acquired immunodeficiency: infectious, allergic, autoimmune, neoplastic, dysbiotic, postviral CFS. In addition, if the allergic syndrome is more common in case of monoherpesvirus infection, the CFS prevails in mixed herpes-viral infections (EBV, CMV, HHV6). Extended testing of the antiviral protection main mechanisms state made it possible to identify the most frequent defects in the functioning of antiviral

immunity: disturbances in induced production of IFNα and IFNγ, deficiency of cytotoxic T lymphocytes, deficiency of natural killer cells, including EKT, and / or inadequate absence of their activation, neutropenia.

We believe that the etiological data obtained during this study allowed us to clarify the prevalence of herpes-viral co-infections over mono-infection, which should be taken into account in the future when mono- or combined etiotropic therapy is prescribed.

Summarizing the obtained data, allow us to outline the goals and further develop the concept of a combined, individualized, immunopathogenetic therapy. The development of interferon and immune therapy methods aimed at antiviral mechanisms restoration of immune defense and the system of interferons will lead to a reduction or complete cessation of the replicative activity of the viruses and will allow the restoration of the immune system control over the herpes viruses persistent in the body, and, consequently, regress the herpes-viral infection and clinical manifestations of the disease.

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ОСНОВНЫЕ КЛИНИЧЕСКИЕ СИНДРОМЫ, АССОЦИИРОВАННЫЕ С АТИПИЧНОЙ ХРОНИЧЕСКОЙ АКТИВНОЙ ИНФЕКЦИЕЙ, ВЫЗЫВАЕМОЙ ВИРУСОМ ЭПШТЕЙНА-БАРР. РАЗРАБОТКА АЛГОРИТМА КЛИНИЧЕСКОЙ И ЛАБОРАТОРНОЙ ДИАГНОСТИКИ

И.В. Нестерова[1,3], Е.О. Халтурина[2,3]

[1]ФГБУ ВО «Кубанский государственный медицинский университет», Минздрава РФ, Краснодар, Россия

[2]ФГАОУ ВО «Первый московский медицинский университет им. И.М. Сеченова», Москва, Россия

[3]Клинико-диагностический центр МЕДСИ на Белорусской, Москва, Россия

Неуклонный рост числа заболеваний, ассоциированных с герпесвирусными инфекциями, является одной из актуальных междисциплинарных проблем современной медицины. Разнообразие клинических и лабораторных «масок» этих инфекций представляет большие сложности в интерпретации полученных клинико-анамнестических и лабораторных данных, а также результатов объективного осмотра пациентов. Это связано с низкой осведомленностью врачей о наличии атипичных хронических активных форм этих инфекций, вызываемых в частности вирусом Эпштейна-Барр, которые затрудняют постановку диагноза и приводят к серьезным последствиям, связанным с персистированием вирусов в организме человека.

Проведены исследования особенностей функционирования системы противовирусной защиты, а также дефекты и нарушения в системе интерферонов у пациентов, страдающих различными моно-, микст-герпесвирусными инфекциями и бактериальными ко-инфекциями. Выявлены основные клинические синдромы, ассоциированные с этими герпетическим инфекциям, а также превалирующие нозологические формы сопутствующих заболеваний. Среди группы пациентов, страдающих моно-герпесвирусными инфекциями лидирующее положение занимает аллергический синдром (55%), в то время как в структуре заболеваемости пациентов с микст-герпесвирусными инфекциями превалируют синдром хронической усталости (85%) и инфекционный синдром (68%). Расширенное тестирование состояния основных механизмов противовирусной защиты, позволило выявить наиболее часто встречающиеся дефекты функционирования противовирусного иммунитета: нарушения индуцированной продукции ИФНα и ИФНγ, дефицит цитотоксических Т лимфоцитов, дефицит естественных киллерных клеток, в т.ч. ЕКТ, и/или неадекватное отсутствие их активации, нейтропению. Выявленные клинические синдромы и особенности функционирования системы противовирусной защиты позволят в дальнейшем разработать концепцию комплексной, индивидуализированной, этио- и иммунопатогенетической терапии.

Ключевые слова: герпесвирусная инфекция, противовирусная защита, интерферон, вирус Эпштейна-Барр

Ответственный за переписку: Нестерова Ирина Вадимовна, доктор медицинских наук, профессор — профессор кафедры клинической иммунологии, аллергологии и лабораторной диагностики ФГБУ ВО «Кубанский государственный медицинский университет», Минздрава РФ, Краснодар, Россия
E-mail: inesterova1@yandex.ru

Нестерова И.В. SPIN: 4714-2488, ORCID: 0000-0002-5339-4504
Халтурина Е.О. SPIN-код: 2813-4952; ORCID: 0000-0002-8948-8983

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