

DIAGNOSIS OF EPSTEIN-BARR VIRUS AND ITS SIGNIFICANCE IN MEDICINE

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Abstract

In this review of the literature, the resources of last ten years about the Epstein-Barr virus, its morphology, the diseases it causes, the diagnosis and treatment of the disease, and the innovative modern diagnostic methods for the diagnosis of the Epstein-Barr virus are widely covered. The development of innovative diagnostic methods and technical convenience have made it possible to detect Epstein-Barr virus early and prevent its spread among the population. For example, the new, modern forms of PCR such as thw real-time PCR (Real-Time PSR), immuno-PCR, Multiplex PCR, Long-range PCR and other innovative technologies are important in the diagnosis of Epstein-Barr virus.

Keywords: Epstein-Barr virus, serological, molecular-biological, ELISA, PCR, asymptomatic carriage, autoimmune diseases, lupus erythematosus, rheumatoid arthritis, vasculitis, chronic fatigue syndrome, Burkitt's lymphoma.

ДИАГНОСТИКА ВИРУСА ЭПШТЕЙН-БАРР И ЕГО ЗНАЧЕНИЕ В МЕДИЦИНЕ

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АННОТАЦИЯ

При анализе этой литературы широко освещаются ресурсы о вирусе Эпштейна-Барр, его морфологии, вызываемых им заболеваниях, диагностике и лечении заболевания, инновационных современных методах диагностики вируса Эпштейна-Барр.. Развитие инновационных методов диагностики и техническое удобство позволили своевременно выявить вирус Эпштейна-Барр и предотвратить его широкое распространение среди населения. Например, в диагностике вируса Эпштейна-Барр важны ПЦР в реальном времени (Real-Time PCR), иммуно-ПЦР, Multiplex PCR, Long-range PCR и другие инновационные технологии.

Ключевые слова: вирус Эпштейна-Барр, серологический, молекулярно-биологический, ИФА, ПЦР, бессимптомное носительство, аутоиммунные заболевания, красная волчанка, ревматоидный артрит, васкулит, синдром хронической усталости, лимфома Беркитта.

Epstein-Barr virus infection (EBVI) is one of the most common human diseases. According to the WHO, about 55-60% of young children (up to 3 years old) are infected with the Epstein-Barr virus, and a large part of the adult population of the planet (90-98%) has antibodies to EBV. EBV is ubiquitous and can infect up to 95% of the world's population. In different countries of the world, the incidence varies from 3-5 to 45 cases per 100,000 population and it is a very high rate(1,4,5). EBVI belongs to the group of uncontrolled infections, in which there is no specific prevention (vaccination), which certainly affects the incidence rate. Epstein-Barr virus was named Epstein-Barr virus in honor of the scientists who discovered it by Anthony Epstein and Anthony Barr(2,12). Epstein-Barr virus infection - acute or chronic infection caused by the Epstein-Barr virus from the family of herpes viruses (Herpesviridae), which has a favorite feature of defeating the lymphoretic and immune systems of the body. According to the International Committee on Taxonomy of Viruses, EBV belongs to the subfamily Herpesvirinae, genus Lymphocryptovirus, type 4 of human herpesvirus. It was

first identified from Burkett's lymphoma cells about 35-40 years ago. The virus has a spherical shape with a diameter of up to 180 nm. The structure consists of 4 components: nucleus, capsid, inner and outer shell. The nucleus contains DNA, consisting of 2 strands, including up to 80 genes. The viral particle on the surface also contains dozens of glycoproteins, necessary for the formation of antibodies that neutralize the virus (Fig.1).

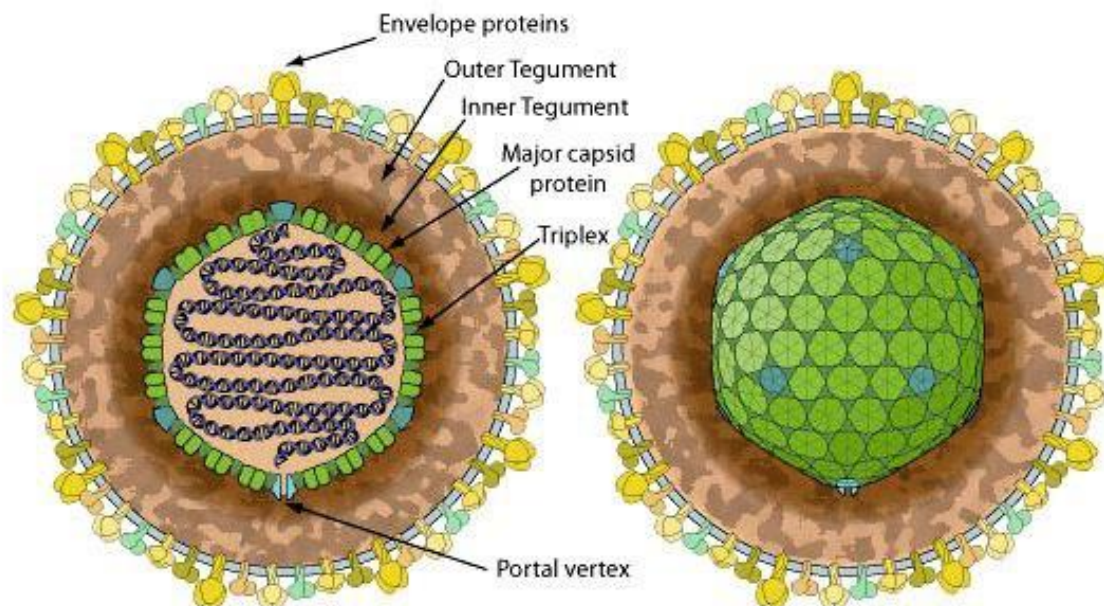


Figure 1. Capsid antigen (VCA); surface antigen (SA); nuclear or nuclear antigen (NA or EBNA); membrane antigen (MA)

In different forms of EBVI, the time of their appearance, importance is not the same and has its own meaning. The Epstein-Barr virus is relatively stable in the external environment, it is quickly killed by drying, exposure to high temperatures, and exposure to common disinfectants(2,3,6). The Epstein-Barr virus can feel good in biological tissues and fluids, when it enters the bloodstream of a patient infected with EBVI, in the brain cells of a completely healthy person, in the cells during oncological processes (lymphoma, leukemia, etc.). The virus has a certain tropism (tendency to infect favorite cells):

- 1) proximity to the cells of the lymphoretic system (there is damage to the lymph nodes of any group, enlargement of the liver and spleen);
- 2) proximity to the cells of the immune system (the virus multiplies in B-lymphocytes, where it can remain for life, as a result of which their functional state is disturbed and immune deficiency occurs); In addition to B-lymphocytes, EBV also disrupts cellular communication of immunity (macrophages, NK -

natural killers, neutrophils, etc.), which leads to a decrease in the body's general resistance to various viral and bacterial infections;

3) proximity to the epithelial cells of the upper respiratory tract and digestive tract, as a result of which children may develop respiratory syndrome (cough, shortness of breath, "false croup"), diarrhea syndrome (loose stools)(1,4,5).

Epstein-Barr virus has allergenic properties, which are manifested by certain symptoms in patients: 20-25% of patients have allergic rashes, some patients may develop Quincke's edema. Particular attention is paid to this feature of the Epstein-Barr virus: presence in the organism. Due to the infection of B-lymphocytes, these cells of the immune system have an unlimited life activity (the so-called "cell immortality"), as well as the ability to continuously synthesize heterophilic antibodies (or autoantibodies, for example, antinuclear). (Antibodies, rheumatoid factor, cold agglutinins). EBV lives permanently in these cells. Nowadays 1st and 2nd stamms of Epstein-Barr virus are now known and they are serologically indistinguishable.

Causes of Epstein-Barr virus infection

The source of EBV infection is a patient with clinical manifestations and a virus carrier. The patient is infectious in the last days of the incubation period, in the initial period of the disease, at the height of the disease, as well as during the entire recovery period (up to 6 months after recovery), and up to 20% of them are infectious. Those who are sick occasionally retain the ability to shed the virus (that is, remain carriers).

Mechanisms of EBVI infection:

- this is aerogenous (airborne transmission), in which saliva and mucus from the oropharynx are infectious and are released during sneezing, coughing, talking, kissing;
- a contact mechanism (contact-household transmission) where saliva from household items (dishes, toys, towels, etc.) appears, but this is not important due to the instability of the virus in the external environment;
- the transfusion mechanism of infection is allowed (during transfusion of infected blood and its preparations);
- digestive mechanism (water-food passageway);
- currently, the transplacental mechanism of fetal infection with the possibility of congenital EBVI development has been confirmed (6,7,14).

Susceptibility to EBVI: Babies (up to 1 year old) rarely get Epstein-Barr virus infection due to the presence of passive immunity (maternal antibodies), the most susceptible to infection and the development of a clinically visible form of EBVI are children aged 2 to 10 years. Despite the diversity of the routes of infection, there is a good level of immunity among the population (up to 50% of children and up to 85% of adults): most people are infected by carriers without developing symptoms, but with the development of immunity. Therefore, patients with EBVI are believed to be non-infectious to others, as many already have antibodies to Epstein-Barr virus(8). In rare cases, EBVI epidemics can still be observed in closed-type institutions (military units, dormitories), EBVI, and especially its frequent manifestations, mononucleosis, is characterized by spring-autumn seasonality. Immunity is strong and lifelong after infection. It is impossible to get sick again with the acute form of EBVI. Repeated cases of the disease are associated with the recurrence or development of the chronic form of the disease and its exacerbation(8).

The route of entry of the Epstein-Barr virus in humans: The entrance to infection is the mucous membrane of the oropharynx and nasopharynx, where the virus multiplies and forms nonspecific (primary) protection. The results of the primary infection are affected by: general immunity, concomitant diseases, the state of the entrance to the infection (presence or absence). The consequences of primary infection can be:

- 1) sanitation (destroying the virus at the entrance);
- 2) subclinical (asymptomatic form);
- 3) clinically defined (manifest) form;
- 4) the primary latent form (in which the multiplication of the virus and its isolation are possible, but there are no clinical signs).

In addition, the virus can enter the bloodstream from the entrance of the infection (viremia) - the patient may have a temperature and intoxication. In the place of the entrance, a "main focus" is formed - catarrhal tonsillitis, difficulty in nasal breathing. Later, the virus enters various tissues and organs with primary damage to the liver, spleen, lymph nodes, etc. Precisely during this period at the same time with the proliferation of lymphocytes, "mononuclear cells of atypical tissues" are also appeared in the (9,13).

The results of the disease can be: recovery, chronic EBV infection, asymptomatic carriage, autoimmune diseases (systemic lupus erythematosus, rheumatoid

arthritis, Sjogren's syndrome, etc.), oncological diseases and congenital EBV infection - death is possible.

Symptoms of EBV infection

Depending on the climate, certain clinical forms of EBVI prevail. Infectious mononucleosis is more common in countries with a temperate climate, including the Russian Federation, and in the absence of immunodeficiency, a subclinical (asymptomatic) form of the disease may develop. Also, the Epstein-Barr virus can cause "chronic fatigue syndrome", autoimmune diseases (rheumatic diseases, vasculitis, ulcerative colitis). In countries with a tropical and subtropical climate, malignant neoplasms (Burkitt's lymphosarcoma, nasopharyngeal carcinoma, etc.) can develop, often with metastases to various organs. In HIV-infected patients, EBVI is associated with hairy leukoplakia of the tongue, brain lymphoma, and other manifestations.

Clinic of some diseases of EBV infection:

1. Infectious mononucleosis, an acute form of the disease with cyclicality and specific symptoms (fever, catarrhal angina, difficulty in nasal breathing, enlarged groups of lymph nodes, liver, spleen, allergic rashes, specific changes in blood). shows itself. Unfavorable signs from the point of view of the development of chronic EBV infection: prolonged nature of the course of infection (prolonged subfebrile state - $37-37.5^{\circ}$ - up to 3-6 months, retention of enlarged lymph nodes for more than 1.5-3 months);

- occurrence of a recurrence of the disease with the return of symptoms within 1,5-3-4 months after the beginning of the primary attack of the disease;

- retention of IgM antibodies (to EA, VCA antigens of EBV) for more than 3 months from the onset of the disease; lack of seroconversion (seroconversion is the loss of IgM antibodies and the formation of IgG antibodies to various antigens of the Epstein-Barr virus);

- not started on time or complete lack of specific treatment.

2. Chronic EBV infection is formed no later than 6 months after acute infection, and if there is no history of acute mononucleosis - it can appear 6 or more months after infection. Often, with a decrease in immunity, the hidden form of the infection turns into a chronic infection. Chronic EBV infection can occur in the following forms: chronic active EBV infection, hemophagocytic syndrome associated with EBV, atypical forms of EBV (recurrent bacterial, fungal and other

infections of the digestive system, respiratory tract, skin and mucous membranes). Chronic active EBV infection is characterized by a long course and frequent relapses. Patients experience weakness, fatigue, excessive sweating, long-term low temperature of 37,2-37,5 °, skin rash, sometimes articular syndrome, pain in the muscles of the trunk and limbs, heaviness in the right hypochondrium, discomfort in the throat, slight anxiety, cough and nasal congestion, in some patients neurological diseases - unexplained headache, memory impairment, sleep disorders, frequent mood swings, tendency to depression, neglect of patients, decreased intelligence. Often, patients complain of an increase in one or a group of lymph nodes, internal organs (spleen and liver) may increase. In addition to such complaints, when questioning the patient, the addition of recent frequent colds, fungal diseases, other herpetic diseases (for example, herpes simplex on the lips or genital herpes, etc.) cough and nasal congestion, neurological diseases in some patients - unexplained headaches, memory disorders, sleep disorders, frequent mood swings, tendency to depression, neglect of patients, decreased intelligence. In confirmation of clinical data, as well as there will be laboratory signs (changes in the blood, immune status, special tests for antibodies). In chronic active EBV infection, the process is generalized with a significant decrease in immunity, and damage to internal organs can lead to the development of meningitis, encephalitis, polyradiculoneuritis, myocarditis, glomerulonephritis, pneumonia, etc. Hemophagocytic syndrome associated with EBV is manifested in the form of anemia or pancytopenia (a decrease in the content of almost all blood elements associated with the inhibition of hemopoietic germs). Patients have fever (wave or intermittent, in which a sudden and gradual increase in temperature may return to normal values), swollen lymph nodes, liver and spleen, liver function abnormalities(10,11)

Atypical forms of EBVI: often this is an unknown fever that lasts for months, years, accompanied by an increase in lymph nodes, sometimes the appearance of joints, muscle pain; another option is secondary immunodeficiency with frequent viral, bacterial, fungal infections.

3. Congenital EBV infection occurs when there is an acute form of EBVI or chronic active EBV infection that occurred during the mother's pregnancy. It is characterized by possible damage to the child's internal organs in the form of interstitial pneumonia, encephalitis, myocarditis, etc. Possible premature birth. Mother's antibodies to Epstein-Barr virus (IgG EBNA, VCA, EA antigens) and

the child's own antibodies (IgM EA, IgM to VCA antigens), which clearly confirm intrauterine infection, can circulate in the blood of the newborn baby (11,15).

4. "Chronic fatigue syndrome" is characterized by constant fatigue that does not go away after a long and proper rest. Patients with chronic fatigue syndrome have muscle weakness, periods of apathy, depressive states, mood swings, irritability, etc. characterized by anger and aggression. Patients are lethargic, complain of memory impairment, mental decline. Patients do not sleep well, and the phase of falling asleep is also disturbed, intermittent sleep is observed, insomnia and sleepiness are possible during the day. At the same time, autonomic diseases are characteristic: trembling of the fingers, sweating, occasional low temperature, additional pains.

The risk group includes people with increased physical and mental work, people in acute stressful situations and people under chronic stress.

5. HIV-related diseases

"Hairy leukoplakia" is manifested in a severe form of the mucous membrane of the tongue and oral cavity, often due to immunodeficiency associated with HIV infection. On the lateral surfaces of the tongue, as well as on the mucous membrane of the cheeks, gums, white folds appear, which gradually merge to form white plates with an uneven surface, as if furrows, cracks and erosive covered with surfaces. As a rule, there is no pain in this disease.

Lymphoid interstitial pneumonia is a polyetiological disease (associated with pneumocystitis, as well as EBV) and is characterized by shortness of breath, ineffective cough. Together with the high temperature and signs of intoxication, also the progressive weight loss is occurred in patients.

6. Oncological lymphoproliferative diseases (Burkitt's lymphoma, nasopharyngeal carcinoma - NFC, T-cell lymphoma, non-Hodgkin's lymphoma, etc.)

Diagnosis of Epstein-Barr virus infection

1. Initial diagnosis is always demonstrated on the basis of clinical and epidemiological data. Suspicion of EBVI is confirmed by clinical laboratory tests, in particular, a complete blood count, which can reveal indirect signs of viral activity: lymphomonocytosis (increased number of lymphocytes, monocytes), less monocytosis in lymphopenia (increased monocytes with a decrease in lymphocytes), thrombocytosis (increased platelets), anemia (decreased red blood cells and hemoglobin), atypical mononuclear cells appear in the blood. Atypical

mononuclear cells (or virocytes) - these are modified lymphocytes, which have some similarities with monocytes according to their morphological characteristics. These are uninucleate cells and they are young cells that appear in the blood to fight viruses. It is the last feature that explains the appearance of EBVI (especially in its acute form). The diagnosis of infectious mononucleosis is confirmed if there are more than 10% of atypical mononuclear cells in the blood, but their number can vary from 10 to 50% or more.

For the qualitative and quantitative determination of atypical mononuclear cells, the leukocyte concentration method is used, which is a very sensitive method. Atypical mononuclear cells appear in the first days of the disease, at the height of the disease their number is maximum (40-50% and more), in some patients their appearance is noted a week after the onset of the disease. In most patients, atypical mononuclear cells continue to be detected within 2-3 weeks from the onset of the disease, in some patients they disappear at the beginning of the 2nd week of the disease. 40% of patients continue to detect atypical mononuclear cells in the blood for a month or more (in this case, it makes sense to actively prevent the process from becoming chronic).

Also, at the initial stage of diagnosis, a biochemical examination of the blood serum is carried out, in which there are signs of liver damage (a slight increase in bilirubin, an increase in the activity of enzymes - ALT, AST, GGTP, thymol test).

2. The final diagnosis is made after special laboratory studies.

1) Heterophilic test - detection of heterophilic antibodies in blood serum, detected in most patients with EBVI. This is an additional diagnostic method. Heterophilic antibodies are produced in response to EBV infection - these are autoantibodies synthesized by infected B-lymphocytes. These include antinuclear antibodies, rheumatic factors, cold agglutinins. They belong to the class of IgM antibodies. They appear in the first 1-2 weeks from the moment of infection, and their gradual increase is characteristic in the first 3-4 weeks, then gradually decreases in the next 2 months and remains in the blood during the entire recovery period (3-6 months). If there are signs of EBVI, if this test is negative, it is recommended to repeat it after 2 weeks. False positive results for heterophilic antibodies in hepatitis, leukemia, lymphoma, can give conditions such as drug use. Also, positive antibodies of this group can be present with: systemic lupus erythematosus, cryoglobulinemia, syphilis.

Serological tests for antibodies to the Epstein-Barr virus by ELISA (linked immunosorbent assay)

IgM to VCA (capsid antigen) - is detected in the blood in the first days and weeks of the disease, it is maximal in the 3-4th week of the disease, it can circulate up to 3 months, and then their number decreases to an undetectable level and disappears completely. Their duration for more than 3 months indicates a long duration of the disease. They are found in 90-100% of patients with acute EBVI. IgG to VCA (capsid antigen) - appears in the blood 1-2 months after the onset of the disease, then gradually decreases and remains at the threshold (low level) for life. An increase in their titer is characteristic of exacerbation of chronic EBVI. IgM to EA (early antigen) - appears in the blood in the first week of the disease, lasts for 2-3 months and disappears. It occurs in 75-90 percent of patients. Keeping high titers for a long time (more than 3-4 months) is alarming in terms of the formation of a chronic form of EBVI. Their appearance in chronic infection serves as an indicator of reactivation. Often they can be detected during primary infection in EBV carriers. IgG to EA (early antigen) - appears in the 3-4th week of the disease, reaches the maximum level in the 4-6th week of the disease, disappears after 3-6 months. The appearance of high titers repeatedly indicates the activation of chronic infection. IgG to NA-1 or EBNA (nuclear or nuclear antigen) - delayed, because they appear in the blood 1-3 months after the onset of the disease. For a long time (up to 12 months), the titer is quite high, and then the titer decreases and remains at a threshold (low) level throughout life. In young children (up to 3-4 years old), these antibodies appear later - 4-6 months after infection. If a person has a clear immune deficiency (AIDS stage with HIV infection, oncological processes, etc.), then these antibodies may not be present. Reactivation of chronic infection or relapse of acute EBVI is observed in high titers of IgG to NA antigen. Enzyme linked immunoassay (ELISA) - this test method is similar to RIA in many respects, but differs from it in the use of additional reagents - AG and AT, targeted enzymes (peroxidase, alkaline phosphatase). Currently, indirect and direct methods of enzyme immunoassay have been developed. This method is widely used in the diagnosis of Epstein-Barr virus (7).

Schemes of interpretation of results. Rules for qualitative diagnosis of EBV infection: Dynamic laboratory examination: in most cases, one antibody test is not enough for diagnosis. Repeated studies are required after 2 weeks, 4 weeks,

1,5 months, 3 and 6 months. The dynamic research algorithm and its need is determined only by the attending physician!

- to compare the results obtained in one laboratory.
- there are no general norms for antibody titers; the result is evaluated by the doctor in comparison with the reference values of a certain laboratory, after which a conclusion is drawn as to how many times the desired antibody titer has increased compared to the reference value. The threshold level, as a rule, does not exceed 5-10 times. High titers are diagnosed at a magnification of 15-30x and above.

PCR diagnosis of EBV infection - DNA of Epstein-Barr virus can be qualitatively determined using PCR

The material for research is saliva or oropharyngeal and nasopharyngeal mucus, epithelial cells of the genitourinary tract, blood, cerebrospinal fluid, prostate secretion. Both EBVI patients and carriers can have a positive PCR. Therefore, to differentiate them, PCR analysis is performed with a certain sensitivity: up to 10 copies per sample for carriers and 100 copies per sample for active infection. In young children (up to 1-3 years old), it is difficult to make a diagnosis by antibodies, because the immunity is not sufficiently formed, so PCR analysis is helpful in this group of patients. The specificity of this method is 100%, it almost eliminates the false positive results. However, since the PCR analysis is informative only during the multiplication of the virus, there is a certain percentage (up to 30%) of false negative results, which is clearly due to the lack of replication during the emergence of the virus depends(13).

Immunogramm or immunological examination of blood

There are two types of changes in the immune status with EBVI: An increase in its activity (increased levels of interferon, IgA, IgM, IgG in the serum, an increase in CEC, an increase in CD16 + - natural killers, CD4 + T-helpers or CD8 + T increase of - suppressors). Immunity disorder or deficiency (decrease in IgG, increase in IgM, decrease in antibody availability, decrease in CD25+ lymphocytes, decrease in CD16+, CD4+, CD8, decrease in phagocyte activity).

Treatment of EBV infection

1) Organizational measures include admission of patients with acute EBVI to the clinic of infectious diseases depending on the severity. Patients with reactivation

of chronic infection are often treated on an outpatient basis. Diet therapy is reduced to a complete diet with mechanical, chemical sparing of the digestive tract.

2) Special drug therapy for EBVI.

Antiviral drugs (isoprinosin from the first days of life, arbidol from 2 years old, valtrex from 2 years old, famvir from 12 years old, acyclovir from the first days of life, in the absence of other means, but less effective). Interferon preparations (viferon from the first days of life, kipferon from the first days of life, reaferon EC-lipind over 2 years old, interferons for parenteral administration over 2 years old). Interferon inducers (cycloferon from 4 years old, neovir from the first days of life, amiksin from 7 years old, anaferon from 3 years old).

Special EBVI therapy rules

1) All drugs, doses, courses are determined only by the attending physician. 2) After the main course of treatment, a long-term maintenance course is required. 3) The combination of immunomodulators is determined carefully and only by the physician. 3) Preparations to increase the intensity of treatment. Immunocorrection (after studying the immunogram) - immunomodulators (thymogen, polyoxidonium, derinat, licopid, ribomunil, immunorix, ronkoleukin, etc.); - hepatoprotectors (carsil, hepaben, hepatofalk, Essentiale, ursosan, ovesol, etc.); - enterosorbents (white coal, filtrum, lactofiltrum, enterosgel, smecta);- probiotics (bifidum-forte, probifor, biovestin, bifiform, etc.);- antihistamines (zyrtek, claritin, zodak, erius, etc.);- other drugs according to the instructions .

Prevention of Epstein-Barr virus infection

There is no special prevention (vaccination). Preventive measures are strengthening immunity, hardening of children, taking precautions when the patient appears in the environment, and observing the rules of personal hygiene. The most common diseases among children are viral. The reason is that the child's immunity is not yet strong enough, not mature, and it is not always easy for him to cope with many external threats. A child can be infected in different ways. EBV is often shed in body fluids, usually saliva. For this reason, infectious mononucleosis caused by a virus is called "kissing disease". Infection can occur during the transfusion of blood and its components, through things and toys that were with the patient, as well as the virus is transmitted from an infected mother to the fetus through the placenta during pregnancy. EBV is easily transmitted

through airborne droplets and from donor to recipient during bone marrow transplantation.

At risk, children under one year of age actively explore the world around them through their mouths, trying to absolutely taste everything and anything that comes to their fingertips. Another "problem" age is children from 3 to 6 years old, who regularly go to kindergarten and have many contacts. The incubation period is from 1 to 2 months, after which bright symptoms characteristic of many viral infections appear in children(14).

However, the virus itself with a complex name is not so terrible, but its consequences are completely unpredictable. In one child, it can be completely ignored, and in another, it causes the development of serious conditions and even oncological diseases. Yevgeny Olegovich warns that treatment of one of the diseases associated with EBV - infectious mononucleosis with antibiotics of the penicillin group can cause serious complications. Usually, when the doctor takes mononucleosis for the usual bacterial tonsillitis, such an appointment is wrong. In this case, exanthema may develop. According to Yevgeny Komarovsky, ordinary children who did not suffer from HIV and other serious diseases of the immune system, Mononucleosis caused by EBV does not need any antiviral treatment, even more, they do not need to be given immediate immunostimulants. A well-known pediatrician is sure that the child's body is able to overcome this threat on its own.

In conclusion

It can be said that the discovery of ELISA and PCR methods, which are used in the early diagnosis of Epstein-Barr virus in medicine, made it possible to detect the disease early, treat the disease, and prevent complications. In the near future, the Republic of Uzbekistan will be widely supported by technological advances such as molecular genetics, digital microbiology and mass spectrometry methods in microbiological laboratory practice, and this will pave the way for scientific achievements and scientific research in the field of microbiology and virology of our country.

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