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CYTOMEGALOVIRUS INFECTION

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Abstract
Cytomegalovirus infection is a widespread human infection with a different transmission mechanism. The variety of clinical manifestations of the disease is due to the ability of human cytomegalovirus to infect almost all cells of the body. Cytomegalovirus often affects people with an immunodeficiency condition. The consequence of this is the continued growth of cytomegalovirus infection not only among children, but also among adults. Cytomegaly is included in the group of "new and mysterious" infections by the WHO Regional Office for Europe.

Keywords: Cytomegalovirus infection, lymphohistiocytic infiltration, cytomegals, localized form, cystic fibrosis, sialoadenitis, hemotransfusion, incomplete replication..

Introduction

More than 100 years have passed since the first descriptions of unknown symptoms appeared in the scientific medical literature, which later turned out to be specific manifestations of cytomegalovirus infection (CMVI). In recent years, CMVI has aroused great interest among doctors of various specialties. Cytomegaly is included in the group of "mysterious" diseases that determine the future of infectious pathology by the WHO Regional Office for Europe. Despite the high level of modern research, the role of CMVI in childhood pathology remains poorly understood. Difficulties remain in diagnosing various forms of CMVI and interpreting research results.

CMVI is a widespread viral disease that mainly affects children of the first three years of life, characterized by a variety of clinical manifestations and a peculiar morphological picture — the presence of cytomegalic cells with inclusions similar to owl's eye and interstitial lymphohistiocytic infiltration.

The priority of the virus discovery belongs to the German pathologist N. Ribbert, who first discovered cytomegalic cells and associated their appearance with compensatory renal hypertrophy in congenital syphilis, and subsequently called them cells similar to protozoa. In 1921, E. Goodpasture and F. Talbot proposed calling the disease childhood cytomegaly, and the cells themselves cytomegals, emphasizing the specificity of giant cell metamorphosis. The terminology has gained general acceptance and is widely used nowadays. Later, in 1926, R. Cole and A. Kuttner proved the viral nature of cytomegaly. In 1932, S. Farber and S. Wolbach called it "a disease caused by a virus of the salivary glands." Of the other synonyms for this disease, the name "disease with inclusion bodies", proposed by S. Gappel and N. McFarlane in 1947, deserves attention. This is where the terms "inclusive cytomegaly" and "disease with cytomegalic inclusions" come from.

In the history of CMVI research, S. A. Demidova et al. there are two periods:
1) the study of the disease exclusively using morphological methods (autopsy);

2) isolation of cytomegalovirus on sensitive cell cultures in 1956 by M. Smith and W. Rowe and further work using this method.

The second period marked the triumph of the lifetime diagnosis of CMVI. Morphological methods of studying cytomegalovirus continue to develop. In recent years, the very direction of scientific research has changed: many of them are devoted to the immunological aspects of the disease, issues of therapy and prevention, elucidation of the causes of cytomegalovirus persistence and latency, viral oncogenesis and teratogenesis; induced CMVI in adults is also being investigated.

The relevance of CMVI is due not only to its wide spread among children of the first years of life and high mortality. Currently, there is an increase in the incidence of CMVI in all countries of the world, which is associated with both an improvement in the quality of diagnosis and a true increase in the disease. According to WHO, in recent years, the incidence of congenital CMVI among newborns varies from 0.3% to 3.0% in different countries, and the number of deaths has reached 19.9 per 1,000 reported cases of CMVI. In the USA, 6,600 children with congenital CMVI are born annually, in Japan — 8000. In Uzbekistan, the frequency of CMVI is not officially registered, and no large-scale population studies have been conducted to study its prevalence.

Cytomegalovirus has strict species specificity. Currently, the following strains have been isolated: Davis, AD169, Kerr, C-87, Esp, Towne. Individual strains of cytomegalovirus have oncogenic properties.

PATHOMORPHOLOGY AND PATHOGENESIS

Tissue reactions in cytomegaly have a rather monotonous two-component character, consisting of cytomegalic cell transformation and interstitial lymphohistiocytic infiltration. The specificity of cytomegalic cells is so significant that their detection does not require virological confirmation of the diagnosis of CMVI.

Taking into account the morphological peculiarity of nodular infiltrates, when they are found in the organs of deceased young children, a reasonable diagnosis of CMVI can be made. Nodular infiltrates are usually found in cases of acute onset of the disease and rapid death. With a localized form, changes in the salivary glands are determined, mainly parotid, less often submandibular and sublingual. In the generalized form, the epithelial cells of many organs and systems undergo cytomegalic metamorphosis. It is possible to form malformations of the intestine and other visceral organs. With brain damage, focal necrosis and calcifications develop. With the completed process, changes in organs are characterized by the development of interstitial or cystic fibrosis with multiple calcifications.

Congenital CMVI is the most common cause of malformations in children, which can be both early, detectable from the first days of life (severe organ lesions), and late, recorded at the age of 2-5 years, occurring with hearing impairment (in 25%), vision (in 8-15%) and kidney pathology.

The high frequency of intrauterine infection with cytomegalovirus is due to the epidemiology of the infection, as well as the peculiarities of the immunity of the pregnant woman, fetus and newborn. The incidence of CMVI depends not so much on the presence of the virus in the mother's body, but on the activity of the infectious process during pregnancy. According to the literature, the frequency of primary CMVI in women during pregnancy does not exceed 1-4%, while intrauterine infection of the fetus occurs in 30-50% of cases, including 5-18% of children with the development of manifest congenital CMVI, which is characterized by a severe course and often ends fatally. Currently, the possibility of superinfection in the presence of several strains of the

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virus is not excluded. Fetal damage can also occur when a latent infection is reactivated in a pregnant woman or when she is infected with a new strain.

Risk factors for the development of intrauterine CMVI are previous abortions, miscarriages, stillbirths, early infant deaths, the young age of the mother, the presence of chronic pathology, and the complicated course of the present pregnancy. Women suffering from chronic genital diseases with a history of frequent acute respiratory viral infections and sore throats are susceptible to infection with cytomegalovirus. At the same time, CMVI in pregnant women may occur without a specific clinical picture — by the type of ARVI or in the form of sialoadenitis.

Unlike other infections of the TORCH group, severe fetal lesions in CMVI can develop in any trimester of pregnancy. An encounter with the virus in the embryonic period can lead to the formation of severe malformations and fetal death. Histogenesis disorders in fetopathies occur against the background of the formation of an inflammatory reaction in the fetus. Before the gestational age of 20-24 weeks (early fetopathy), when the fetus is unable to localize the infectious process, a generalized disease develops with circulatory disorders, dystrophic and necrobiotic processes. The result may be changes resembling embryonic malformations (hydrocephalus, hydronephrosis, cystic changes in organs and tissues). Later fetopathies are characterized by more mature inflammatory reactions with a tendency to localization of the process (hepatitis, nephritis, encephalitis and myocarditis).

Cytomegalovirus has a tropicity to neurons and neuroglia. It is known that immature glial cells in the subcentricular region are most susceptible to cytomegalovirus. The ability of the virus to persist for a long time in the central nervous system causes the development of specific encephalitis in the fetus, which often results in neurological defects: mental retardation, epilepsy, sensorineural deafness. Cytomegalovirus is also tropic to other tissues: epithelial cells of the salivary glands, renal tubules, vascular endothelium, leukocytes (lymphocytes, macrophages, neutrophils), megakaryocytes, fibroblasts. This extended tropicity explains the polymorphism of the clinic and the development of immunosuppression.

It has been established that the effect of the virus on the fetus can be indirect and lead to various disorders in the placenta: disorders of uteroplacental circulation, impaired metabolism of amniotic fluid, deviations in the evolutionary formation of the placenta. At the same time, clinical symptoms may be manifested by nonspecific somatic disorders: shortening the duration of pregnancy and premature delivery, the birth of a child with symptoms of intrauterine hypoxia, signs of intrauterine hypotrophy, morphofunctional immaturity, general intrauterine development delay.

Cytomegalovirus differs from other representatives of the herpes virus family by a significantly lower reproduction rate. The ability of the virus to replicate in the cells of the immune system and induce its insufficiency causes the creation of a background for the development of recurrent septic, fungal and viral diseases. Damage to the immune system at the stages of early ontogenetic development can lead to an unusual formation of immune reactions and an inadequate immune response in late ontogenesis. This is manifested by delayed pathology, the development of allergic and autoimmune diseases.

Cytomegalovirus can remain latent in the human body for a long time without having a significant negative effect on the growth and development of a child, which is associated with the production of proteins blocking receptors of the 1st and 2nd classes of the HLA system. This leads to a violation of the transmission of signals to proliferation and differentiation in the entire immune

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response system, including antibody synthesis systems, IFN, cytotoxic lymphocytes with CD8+ phenotype, etc.

Currently, it has been proven that in the case of the development of CMVI in a seropositive lactating woman, natural feeding should not stop, since at the same time the child receives antibodies to cytomegalovirus from the mother's milk. Passive specific immunization of a newborn prevents active replication of the virus and contributes to the development of an asymptomatic form of the disease.

In 30-50% of cases, acquired CMVI develops during childbirth or in the postnatal period. It can have various clinical manifestations: from fever, sialoadenitis, mononucleosis-like syndrome, gastrointestinal tract damage to the development of generalized forms with consistent involvement of all organs and systems in the process.

The mononucleosis-like form begins acutely with an increase in body temperature and the appearance of symptoms of intoxication. Patients have sore throats, hepatosplenomegaly, enlarged cervical and submandibular lymph nodes.

Localized CMVI — sialoadenitis: the virus is detected in the tissues of the salivary glands (more often parotid, less often submandibular and sublingual).

Generalized CMVI: many organs and systems are consistently involved in the process. In such cases, sepsis is suspected, and patients often receive intensive antibacterial therapy.

Forms of generalized CMVI:

• the pulmonary form is manifested by persistent, often whooping cough, and the gradual development of pneumonia. The X-ray shows an altered vascular pattern, sometimes lung cysts are detected;

• The cerebral form is characterized by meningoencephalitis. In the future, there is a lag in mental development. Calcifications are found on the X—ray of the skull, mainly in the periventricular areas of the brain;

• the renal form is rarely diagnosed during the life of a child, as it has a poor clinical picture. Often, the only symptom of the disease is the appearance of changes in the general urine analysis: the presence of protein, an increase in the number of epithelial cells and the presence of cytomegalic cells in the urine sediment;

• the gastrointestinal form is characterized by bloating, pallor of the skin, persistent vomiting, frequent loose stools without significant pathological impurities, lagging in physical development. In the coprogram, a large amount of neutral fat is detected in connection with a lesion of the pancreas by the type of polycystic degeneration;

• the hepatic form manifests itself in the form of subacute cholestatic hepatitis.

The maximum mortality from CMVI occurs in the first 3-4 months of life. Acute CMVI can turn into chronic or latent forms that can be reactivated.

Currently, acquired CMVI has become increasingly detected in children and adults from among patients after hemotransfusion and organ transplantation, HIV-infected, oncological patients and other categories of immunologically compromised persons. This aggravates the course of the underlying pathology and contributes to the development of complications.

Until now, infection with cytomegalovirus in blood recipients remains one of the serious problems. In our country, donors are not being examined for CMVI yet. At the same time, it is known that from 15% to 40% of children and 2-3% of adults are infected with blood transfusion from seropositive donors. Even more difficult problems are related to organ transplantation. After

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transplantation, 38-96% of patients have an active form of CMVI, in which it is possible to involve each organ or system in the infectious process. For example, during bone marrow transplantation, cytomegalovirus infects 5% of recipients, and the most severe complication is interstitial pneumonia, which is diagnosed in 10-15% of cases. The sources of infection in transplant patients are not entirely clear. Since endothelial cells are often infected with cytomegalovirus, they can play an important role in the development of infection after transplantation. There is a theory that one of the reasons for transplant rejection is CMVI activation.

Children with acquired CMVI are often infected by airborne droplets and household contact when visiting preschool institutions or from older children in the family. It has been proven that the frequency of virus detection in organized children is significantly higher than in children who do not attend organized groups. With such an infection, the disease more often occurs with a clinic of respiratory infection or infectious mononucleosis. Children infected with cytomegalovirus often suffer from respiratory diseases and form a contingent of children who are often and long-term ill. The variety of clinical symptoms of the disease caused by damage to various organs, and the commonality of clinical manifestations of CMVI with manifestations of other herpetic infections do not allow diagnosing CMVI only by clinical signs. Therefore, laboratory research methods are of great importance at the present stage. In addition, CMVI often occurs under the "mask" of other diseases, which makes it difficult to diagnose and treat it.

DIAGNOSIS OF CYTOMEGALOVIRUS INFECTION

Laboratory diagnostics of CMVI is based on the detection of the virus itself or its DNA, its antigens, as well as specific antibodies to the virus in the studied samples. The main methods of laboratory diagnosis of CMVI are cytological and histological studies, virological and molecular biological methods, enzyme immunoassay, immunofluorescence reaction, immunofluorescence detection of cytomegalovirus antigens and determination of early proteins of its replication.

1. The cytological method is the detection of specifically altered cells in the test material stained with azur-eosin or hematoxylin-eosin. Urine, saliva, cerebrospinal fluid, sputum, lavage fluid, vaginal and cervical secretions can be examined. The presence of cytomegalic cells in the biopsy of the affected organ or in the pathological and anatomical material is the final proof of the presence of CMVI. The diagnostic value of the method is limited by the low sensitivity of lifetime diagnostics. Therefore, it is recommended to conduct multiple studies of urine and saliva — at least 3 studies per day for 3-5 days. If the results are negative, the study is repeated after a week. The method allows you to identify an infection only with the maximum severity of the process.

2. Histological examination of the afterbirth is considered the "gold standard" for the diagnosis of intrauterine infection. At the same time, focal ischemic infarcts, hemorrhages in the interstitial space, fibrinoid necrosis of the basal lamina and in the stroma of large villi, signs of placental hyperplasia, productively proliferative villusitis and focal basal deciduitis, vascular thrombosis and the presence of cytomegalic cells of the "owl's eye" type in placental tissues are detected.

3. Virological methods are based on the infection of monolayer cultures of human embryo fibroblasts and diploid cultures of human lung cells with the studied material, followed by microscopic determination of the cytopathogenic effect of the virus on cells. Blood, urine, saliva, bronchial aspirate, blood serum, and sectional material are used to infect cell cultures. Virological methods are highly specific, but it should be borne in mind that the isolation of the virus from urine or saliva is not a sign of acute infection, since the virus can be detected in these biological

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materials for several months and even years after recovery. The presence of the virus in culture does not allow distinguishing between primary and recurrent infection, although it confirms virus transmission, which is very important for verifying the diagnosis in newborns. Given the thermal stability of the virus, the samples taken should be protected from freezing.

4. Molecular biological methods. Molecular hybridization is the detection of viral DNA directly in the studied samples. Polymerase chain reaction (PCR) is based on the detection of the cytomegalovirus genome in samples of material obtained from the patient. Blood serum, urine, saliva, lacrimal and cerebrospinal fluids, biopsies are examined. PCR makes it possible to detect viral DNA in the test material and determine the number of copies of the pathogen in the sample, which makes it possible to monitor changes in viral load during the disease and when prescribing specific therapy. This is a highly sensitive and highly specific method, since it can be used to detect both active and latently present virus in the material at the level of one viral genome per million cells studied. The advantages of the PCR method are the possibility of early detection of the pathogen in the patient's body (even before the formation of an immune response), as well as the possibility of detecting infectious agents in latent forms of the infectious process. The presence of the pathogen in saliva serves as a marker of infection and does not indicate significant viral activity. The detection of cytomegalovirus DNA in urine confirms the fact of infection and viral activity, and the presence of DNA in whole blood indicates a high replication of the virus and its etiological role in the existing organ pathology.

5. Enzyme immunoassay is used to determine antibodies to cytomegalovirus of IgM and IgG classes with an assessment of their avidity level. Avidity is an indirect sign of the functional activity of antibodies. In the acute period of infection, specific IgMs are formed first, and a little later, specific low—level IgGs. As the severity of the process subsides, the avidity of IgG increases, highly avidious immunoglobulins are formed, which completely replaces the synthesis of IgM. Thus, the serological markers of the acute phase of the infectious process are IgM and low-level IgG. However, since the disease develops more often in people with immunological insufficiency, an increase in titer is not always recorded, especially in premature newborns.

6. The immunofluorescence reaction is used to establish the activity of the infectious process in blood leukocytes. It is based on the detection of fluorescent antibodies. Fluorochrome-labeled antibodies do not lose their ability to bind to the corresponding antigens, and this causes them to glow in blue-violet rays, the source of which is a mercury-quartz lamp. The presence of antigen glow in the nucleus and in the cytoplasm of cells makes it possible to detect pp72 and pp65 proteins. The appearance of the pp72 protein indicates a rapid stage of cytomegalovirus replication. The pp65 protein belongs to the late structural proteins. Its detection indicates the complete replication of the virus or the presence of an active virus in the body. If there is a glow only in the nucleus and there is no glow in the cytoplasm of cells, the protein of the rapid replication stage pp72 is released. This is an indicator of incomplete replication of cytomegalovirus and indicates the presence of the virus in an inactive state. This protein is usually observed in latent or subacute CMVI.

7. Immunofluorescence detection of cytomegalovirus antigens in infected cell cultures or in peripheral blood mononuclear cells, which are treated with monoclonal antibodies to α- or β-cytomegalovirus proteins, and then examined under a microscope in ultraviolet light. The method makes it possible to detect viral antigens in saliva, urine, cerebrospinal fluid, and sectional material. Its specificity is 60-70%.

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8. Determination of early cytomegalovirus (pp65) replication proteins in peripheral blood lymphocytes or oropharyngeal mucosal smears by immunocytochemistry. Currently, this method is proposed as the "gold standard" and an early marker of CMVI.

Tests for specific proteins 70-76 and 90-95 kDa are used abroad for diagnosis. The immune response to the above proteins is detected for at least 5 years from the moment of seroconversion. The 73 kDa protein test can be used as a differential test, since a decrease in the amount of this protein indicates a decrease in the acute process. There is evidence in the Russian literature about the possibility of using the titer of R-proteins in blood serum to assess the dynamics of the condition, severity and generalization of the pathological process in CMVI. When evaluating the results of serological studies, it should be remembered that cytomegalovirus has antigenic similarities with other viruses of the Herpesviridae family (Epstein—Barr virus, Varicella zoster, etc.). In addition, there is evidence that antibodies to cytomegalovirus are similar to rheumatoid factor (95% homologous amino acid composition), which may cause cross-reactions.

Treatment

Specific therapy in children with CMVI should be carried out only after verification of the diagnosis, confirmed by data from clinical, immunological and virological studies. Unfortunately, none of the modern methods of treatment allows you to completely get rid of cytomegalovirus, which, when ingested, remains in the human body forever. Therefore, the goal of CMVI treatment is to eliminate the symptoms of the acute form of the disease and keep the virus in a passive state. If CMVI is asymptomatic and the immunity of the virus carrier is normal, then there is no need for treatment.

Currently, the treatment of CMVI in the acute period includes etiotropic and post-syndrome therapy. Etiotropic therapy includes antiviral drugs (virostatics), specific hyperimmune anticytomegalovirus immunoglobulin and IFN. Etiotropic therapy can be implemented only in the phase of virus replication, in the presence of clinical manifestations and the identification of specific low-level IgG or IgM. The realization of the pathogenic potencies of cytomegalovirus is closely related to the state of the body's defense mechanisms. With CMVI, an immunodeficiency condition is formed, therefore, immunomodulatory and immunostimulating therapy are widely used in treatment.

Modern approaches to immunomodulatory therapy include the use of various targeted immunobiological drugs, such as immunoglobulins for intravenous administration, preparations of recombinant cytokines, colony stimulating factors and monoclonal antibodies to a number of pro-inflammatory mediators of the immune system, taking into account their importance in the pathogenesis of the disease.

IFNs are the most important mediators of the immune system involved in protecting the body from infections. The IFN system is close to the immune system in importance, and even surpasses it in versatility. It is this versatility that makes the IFN system the most important factor in nonspecific resistance of the body. There is evidence that IFNs of various types regulate antibody formation, while having a twofold effect on the human immune system.

Currently, IFN inducers in age-related doses under virological control have become widely used. These drugs not only exhibit antiviral and anti-inflammatory effects, but are also characterized by low toxicity with no side effects. Endogenous IFN, produced in response to the introduction of

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interferogens, does not have antigenicity, its synthesis in the body is balanced and undergoes control and regulatory mechanisms that protect the body from oversaturation.

Currently, it has been proven that vitamins are universal regulators of metabolic processes in the body. The specific function of most vitamins is that the coenzymes or prosthetic groups formed from them are part of the active centers of enzymes and, thus, take part in the mechanisms of enzymatic catalysis of numerous metabolic reactions underlying almost all processes of vital activity and body functions. CMVI leads to a sharp depletion of compensatory and adaptive mechanisms, for the adequate provision of which significant resources of vitamins and trace elements are needed.

In recent years, the influence of probiotics on the immune system has become increasingly important. It has been proven that the gastrointestinal tract is an important part of the human immune system. This is evidenced by many facts, one of which is the presence of a significant part of the lymphoid tissue in the intestine. Four key interrelated components are involved in the implementation of immune mechanisms at the level of the intestinal tract: normal microflora; lymphoid tissue associated with the intestinal mucosa; cytokines as factors of intercellular interaction, as well as products of secretion of immunocompetent and phagocytic cells. The addition of probiotics to complex therapy in normal age-related doses causes an immunomodulatory effect.

Currently, nucleoside analogues are widely used. The principle of action of purine and pyrimidine analogues is that they prevent the incorporation of nucleotides into cytomegalovirus DNA and, therefore, are effective inhibitors of its replication.

In severe forms of CMVI, virostatic drugs are recommended: ganciclovir, foscarnet. Their use in children's practice is limited by age-related contraindications due to the development of complications: leukopenia, anemia, thrombocytopenia, toxic hepatitis, nephritis and encephalopathy. Virostatic drugs are often combined with a specific immunoglobulin.

As a replacement therapy, it is possible to use normal human immunoglobulin enriched with antibodies to cytomegalovirus. In severe generalized form, complicated by secondary bacterial infection, Pentoglobin is prescribed. In the absence of specific immunoglobulins, complex immunoglobulins can be used for intravenous administration.

Valganciclovir is intended for induction and maintenance therapy of cytomegalovirus retinitis in HIV-infected patients, for the prevention and treatment of CMVI in recipients of solid organ and bone marrow transplants.

When a bacterial infection is associated or complications are threatened, antibiotics from the groups of cephalosporins of the II and III generations, aminoglycosides, macrolides, fluoroquinolones, etc. are prescribed. according to generally accepted schemes and in dosages appropriate to the age of the child. In severe forms of CMVI, corticosteroid hormones are indicated.

Organ pathology requires additional treatment. When reactive hepatitis occurs, hepatoprotective agents are prescribed: ursodeoxycholic acid preparations, glycyrrhizic acid with phospholipids, artichoke leaf extract, etc. They not only protect the endoplasmic reticulum of hepatocytes, but also stimulate regeneration processes, enhance intracellular metabolism by regulating the level of plasma proteins, and also increase the level of cytochrome P-450 in the microsomal hydroxylation system, which plays an important role in the metabolism of drugs and detoxification of poisons.

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Adsorbents of various groups and derivatives of ursodeoxycholic acid are used to relieve symptoms of cholestasis.

In the presence of impaired digestion of proteins, fats and carbohydrates, enzyme preparations are used for substitution purposes, which stimulate the release of their own enzymes by the pancreas, stomach and small intestine and lead to an improvement in the functional state of the gastrointestinal tract.

CONCLUSION

An in-depth understanding of the role of cytomegalovirus infection in the formation of multiple organ pathology will allow a new assessment of many known diseases in order to improve their diagnosis and therapy.

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