DOI: 10.5281/zenodo.2590026
UDC: 616.98:578.825.12

The role of cytomegalovirus in the development of opportunistic infections

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Manuscript received November 02, 2018; revised manuscript February 05, 2019

Abstract

Background: About one century ago, was found and described a new virus, which, due to its particular way of damaging cells, was called cytomegalovirus. Human is the only natural source of cytomegalovirus infection. The relevance is that it is a widespread pathology, and due to its ability to "disguise" in the human body, remains unnoticed until the "defect" appears in the body's immune system. It is especially dangerous for pregnant women, children and people with immunodeficiency. It is one of the most common infections that cause pathology in the fetus and newborns, which, in turn, leads to serious consequences, from disability to child death. There are many ways of cytomegalovirus transmission: airborne, parenteral, domestic contact, sexual and vertical (transplacentally, with aspiration of secretions from the birth canal and natural feeding). The virus is able to have a direct and indirect effect on the body. It is able to independently induce immunosuppression. The article describes the epidemiological data, pathogenesis, clinical manifestations, and modern methods of diagnosis, treatment and prevention of cytomegalovirus infection. Also, some diagnostic problems in immunosuppressive organisms are described.

Conclusions: Due to its consequences, namely, children`s disability, death and immunosuppressed people, cytomegalovirus has become a demographic problem. A high infection frequency indicates a low level of social development of the population. More public awareness is needed on the transmission and possible consequences of cytomegalovirus infection.

Key words: cytomegalovirus, opportunistic infections, immunosuppression.

Introduction

Cytomegalovirus (CMV) is an opportunistic pathogen that, after the primary infection, causes lifelong latent infection without any clinical manifestations in immunocompetent organisms. It causes severe diseases in weakened organisms, namely, newborns, patients receiving antitumor chemotherapy, transplant recipients and HIV patients. CMV has some mechanisms by which it avoids the detection and destruction of the host immune system [1]. A CMV is a ubiquitous virus. Numerous researchers all over the world have obtained data indicating that the population has a large number of virus carriers and individuals with a hidden form of CMV. The proof of human infection is the presence of CMV antibodies in the body. There is information about the wide spread of CMV in the human population, the upward trend, the associated morbidity, and its increasing importance in human pathology [2, 3, 4, 5, 6]. Most of the world population (65 to 90%) is infected with a pathogen throughout life. The infestation percentage depends on the socioeconomic status, geographical location and education [7]. It has been observed that seropositivity and virus carriage are more common in developing countries.

According to the decision of the WHO European Office, cytomegalovirus infection (CMVI) is included in the list of "new and mysterious diseases that determine the future of infectious diseases" [8]. The relevance of CMV infection is that it is a widespread pathology, and due to its ability to "disguise" in the human body, it remains unnoticed until the "defect" appears in the body's immune system. The increase in the number of people with immunodeficiency is of current interest. These include people who take immunosuppressants and cytostatics, patients who suffer from malignant neoplasms and HIV infection [3, 9]. Studies have shown that the development of CMVI during the treatment with cytostatics results in death in 80% of cases [10]. CMV is one of the most common infections which cause pathology in the fetus and newborns, which, in turn, leads to serious consequences, from disability to child death [11]. This indicates the presence of a demographic problem. The infection of the pregnant women during the first trimester of pregnancy is especially dangerous. Such cases are less common, but the fetus pathology is very pronounced [9, 12]. The exacerbation of chronic infection and superinfection with another strain of CMV is also dangerous [3]. It has been established that during blood transfusion and organ transplantation, CMV infection can also be transmitted.

History

In 1881, at a meeting of the Society of Physicians of the *Lower Rhine* region, the German pathologist H. Ribbert, for the first time described the histological picture of the neonatal nephritis with congenital syphilis. He found hypertrophied renal tubules with unusual giant cells containing nuclear inclusions. He suggested a protozoan etiology of the inclusion. In 1904 he described similar cells in other neonatal organs. In 1920–21 E. Goodpasture and P.Talbert

suggested that the etiology of this infection was viral, since the lesion was similar to herpes virus and chickenpox virus. The changes in the normal epithelial cells found in the liver, kidneys and lungs are due to chronic inflammation. This characteristic picture was called "cytomegaly". In 1925, for the first time, such cells were found in the body of an adult, viz. in a man who died as a result of complications of liver abscess and ulcerative colitis. In 1926 Cole and Kuttner found similar changes in the salivary glands of rats and gilts. The unsuccessful attempt to infect other animal tissues with infected human secretions proved the specificity of tropism specifically to the salivary gland epithelium. Fetterman (1952) found that cytomegalic inclusions can be discharged during the whole life, being found in the urine. In 1954 Smith isolated a pure virus culture from the salivary gland epithelium in rats, and later from the human salivary glands. Rowe found this virus in the adenoids of children. In subsequent years, intracellular inclusions characteristic of cytomegaly were found in the tissues of the liver, spleen, brain, retina of sick newborns and infants. Clinically, these changes manifested as hepatosplenomegaly, icterus, chorioretinitis, microcephaly with mental retardation, motor disorders, cerebral calcification. In 1960 Weller introduced a new nosology – cytomegalovirus infection. In 1960-1970, due to the active study of this pathogen, the modes of transmission (natural and artificial) were determined, and the fact that most people remain infected after initial contact [13, 14, 15].

Epidemiology

Human is the only natural source of CMV infection. The age of CMV infection depends on the geographical location, socioeconomic status, culture and education of the population. In developing countries most children become infected with CMV infection in the first years of life, therefore, in early youth, 100% of the adult population is seropositive. In developed countries, only 50% of young people of intermediate socioeconomic status are seropositive. This observation has important implications for the epidemiology of congenital CMVI. Inasmuch as a CMV- seronegative woman of childbearing age has a serious risk to be infected during pregnancy, this can cause a high probability of intrapartum infection of the fetus as well as the birth of a baby with some congenital infection symptoms. Cases of congenital CMVI in infants from mothers who have been infected before pregnancy are caused by reactivation or reinfection with another virus strain. Its main biological properties have a lifelong persistence (in the vascular endothelium, liver, spleen, salivary glands, brain and kidneys), and reactivation in the human immunosuppressed organism [7, 16, 17]. It is important to note that there are many ways of CMV transmission: airborne, parenteral, household contact, sexual and vertical (transplacentally, aspiration of secretions from the birth canal and breastfeeding). This infection is also called "kissing disease", as it is often transmitted through sexual contact, therefore it can be considered a problem of young people [18]. In turn, blood transfusion and organ transplantation are also important ways of CMV transmission. Thanks to blood screening, the number of cases of morbidity and mortality of premature babies was reduced due to transfusion-induced CMV infection [13]. According to some researchers, infectious diseases are detected in 50-60% of full-term newborns and 70% of premature newborns [19]. CMVI is one of the most common intrauterine infections that cause severe pathology, even the child death [11]. More than 50% of breast-fed infants of CMV-seropositive mothers are infected with CMV [20]. The uninfected children have a high risk of infection in kindergarten. According to some studies, about 80% of preschool children are CMV-seropositive. After all, the virus is easily transmitted to susceptible children through saliva, urine and other contaminated objects. Being infected in the kindergarten, children can transmit the infection to their parents [21, 22], which plays an important role in the epidemiology of CMV infections in young parents [23]. It is considered that the sexual transmission of CMV is prevalent in the adult population [18], but given the fact that the virus is found in saliva, vaginal secretions and semen, it is difficult to determine which particular way of transmission prevails. Serodiagnosis of donor and recipient blood before and after transfusion is evidence, that CMV is also transmitted parenterally. A research was conducted on blood screening before transfusion. It revealed that the rate of CMV transmission to premature newborns was reduced [13]. Often, the clinical manifestations of CMVI are found in previously infected individuals, which is the reactivation of the latent form or reinfection with a new strain. In HIV patients, cytomegalovirus affects the organs during the stages of progressive immunosuppression, viz, in the AIDS stages, which either do not receive or do not respond to antiretroviral therapy (ART). Other risk factors include the presence of associated opportunistic infections (pneumocystic pneumonia, toxoplasmosis, histoplasmosis, tuberculosis, etc.), high levels of CMV and HIV viremia in plasma [24].

Morphological and biological features of CMV

Cytomegalovirus: Herpesviridae family, Bethaherpesviridae subfamily, Cytomegalovirus genus [25]. Morphological and biological properties are similar to herpes simplex virus type 1. CMV belongs to the human herpes virus type 5. CMV has the largest double-stranded linear DNA genome from the entire Herpesviridae family. The virus consists of an icosahedral capsid covered with a tegument and a bilipid outer envelope [13, 26].The approximate size of spheric virion is 200-300 nm [26]. The cubic nucleocapsid contains 162 of capsomers. The surface and capsid glycoproteins are distinguished in the virus structure. The glycoproteins gB, gO, gN, gH, gL, located on the membrane surface, are involved in the attachment and penetration into the host cells. Protein gB is the initiator of attachment [27]. The remaining glycoproteins are involved in the cell-virus immune response [27]. The proteinkinase is found in CMV.

It phosphorylates ganciclovir (antiviral drug), which is very important in the treatment of CMVI. When a kinase mutates, the resistance to therapy develops [13, 28]. CMV is characterized by: low virulence, the ability to suppress cellular immunity, a long cycle of reproduction and the lowest cytopathogenic activity, in contrast to herpes simplex virus. Like other representatives of herpes viruses, CMV has the ability to infect mononuclear cells and lymphocytes. It replicates in cell culture (in vivo), but slowly [26].

CMV is able to encode more than 200 protein structures [13]. The functions of most of these proteins remain unclear, but it is known that they are divided into functional and structural proteins. Some functions of the functional proteins have been established: UL16 protein inhibits natural killer (NK) cells; UL24 induces cell cycle arrest; TRS1 inhibits the process of autophagy of affected cells; UL36 inhibits cell apoptosis; US2 destroys the components of the major histocompatibility complex (MHC) class 2, preventing the recognition of CD4 + lymphocytes; US3 prevents maturation and transport of MHC class 1 molecules; phosphoprotein 65 (pp65), located in the tegument, inhibits the cascade of interferon production, which provides an inborn antiviral immunity [26].

Pathogenesis

CMV has a direct effect on the body. Using the above surface glycoproteins, it attaches to specific receptors of the cytoplasmic membrane of the host cell [26]. In respect of the vital activity of the virus, the intracellular parasitization is necessary, as it has adapted itself to penetrate the cells through a few ways [26]. CMV penetrates through viropexis or fusion of capsid with cytoplasmic membrane. Being inside the cell, virus replication begins, which consists of 3 phases. The super early phase lasts 2-4 hours after infection. During this period nucleocapsid proteins are synthesized to ensure penetration into the nucleus and onset of viral replication. The viral nucleocapsid DNA activates the major immediate early gene (IE). This gene encodes a protein that is the main regulator of virus transcription and activation. During replication, antigens are synthesized and accumulated in the nucleus, viz. the virus grows up. Next the 24 hour early phase ensues. It begins with the synthesis of a new viral DNA, DNA polymerase and enzymes that are necessary for the production of new virions. As a result, the newly replicated DNA is coated with a capsid. Then the late phase begins, namely, the escape of the virus into the cytoplasm of the host cell. Here it is enriched with the secondary coat – envelope. The envelope is synthesized in the endoplasmic reticulum and the Golgi apparatus [13, 14, 26]. Depending on the type of the affected cell, 2 variants of late phase development are possible, but the result in both cases is cell lysis. In the epithelium of mucous membranes – virus exocytosis occurs, while in lymphocytes, monocytes and fibroblasts – latent persistence is found. In the late period, the virus cannot be recognized due to a weak expression of IE gene [26, 27, 28, 29]. The activation of the infectious process can occur with the differentiation of monocytes into macrophages. This occurs during an active infectious process. The viral fragments are recognized by professional antigen-presenting cells, namely dendritic cells, macrophages, B-lymphocytes, CD8 + and CD4 + lymphocytes. Being activated, they release pro-inflammatory cytokines and activate NK and antigen-specific T-helpers. In turn, NK lyses cells in which the MHC class 1 disappeared due to the virus. Pathologies resulting from direct action are described in the section *Clinical manifestations*. CMV also has an indirect effect on the body, causing its immunosuppression via the following mechanisms: 1) preventing the antigen presentation of CD8+ and CD4+ cells, viz., suppressing their cytotoxicity; 2) preventing the expression of MHC 1-2 molecules on the cell surface; 3) viral protein blocking of the cytotoxic action of NK [12]. Due to the suppression of T-lymphocytes and B-lymphocytes functions, the antibody synthesis diminishes (IgM, IgG). This misleading aspect results in diagnosis difficulties. A discordance is observed between the patient's condition and the process activity, especially in cases of AIDS and allogeneic immunosuppressions [30]. This manifests as transplant rejection and superinfection [10].

Clinical manifestations

Clinical manifestations are very variable due to the tropism to the multitude of body tissues, as well as different sensitivity of these tissues to the virus action. This is not uncommonly misleading when making diagnoses, being disguised as other nosologies. The epithelium of the mucous membranes of the respiratory and intestinal tracts is the most sensitive, as well as the epithelium of the bile ducts, neuroglial and hematopoietic cells.

CMV in *immunotolerant humans*, is manifested as CMV mononucleosis or sialoadenitis. CMV mononucleosis begins with general symptoms of intoxication, fever, as well as sore throat and pain in the projection area of the salivary glands. Objectively, swollen cervical and submandibular lymph nodes are determined and enlarged liver by2-3 cm from the costal arch. In sialoadenitis, on the background of subfebrile temperature, the parotid salivary glands are bilaterally impaired.

In *children*, depending on the infection period, CMV can manifest itself in several forms: 1) congenital (intrauterine infection), the symptoms appear in the first 2 weeks of life; 2) perinatal (infection during childbirth or neonatal period); 3) acquired (infection of children from 1 month to 2-5 years) [13, 31]. In the congenital form, 90% of babies lack clear signs of CMVI. This happens when an infected woman gets pregnant. Such children have a high risk of developing complications, such as developmental delay and neurosensory deafness. The frequency of the latter is about 15%, [32, 33]. In the congenital form, only 10% of newborns have obvious symptoms of CMV lesion. Of these, 40–90% have hepatitis, neurological disorders, developmental delay, cerebral palsy, microcephaly, and mental retardation [34, 35, 36]. The cases of sensorineural hearing loss amount to

about 35-65% [37]. This type of CMVI is called "cytomegalic inclusion disease". This type also develops in the case of primary infection of the mother during pregnancy. The aspect of the newborn is "blueberry muffin baby", due to the defeat of the hematopoiesis cells and the development of thrombocytopenic purpura [13]. The CNS impairment occurs, namely, cerebral atrophy, chorioretinitis with optic nerve atrophy, microcephaly, ventriculomegaly and the presence of intracerebral calcificates. At the same time, a little more than 30% of newborns are premature. Different combinations of syndromes are characteristic [38, 39, 40]. Sucking and swallowing disorders are objectively revealed, as well as strabismus, epileptic seizures, paraparesis, plegia and muscular hypotonia is replaced by hypertension. There is an assumption that CMV influences the development of neurological symptoms in Down`s syndrome [41]. In the case of perinatal infection some conditions are characteristic, such as neonatal cholestatic hepatitis, hematological disorders, lymphadenopathy, focal nephritis and pneumonitis (viz., atypical inflammation of lung tissues). In acquired infection, mononucleosis syndrome, acute CMV hepatitis, or prolonged fever syndrome are possible. The outcome of an acute process in any tissue is the formation of calcifications and interstitial fibrosis [42].

In patients with *post-transplant immunosuppression*, any kind of CMV infection has a more severe course with a high incidence of lethal outcome, and usually occurs in the first 120 days after the intervention. The clinical manifestations depend on the type of transplant and the degree of immunosuppression. Bone marrow recipients most often develop interstitial pneumonia, hepatitis, and esophago-gastro-duodenal impairment. In the case of recipients of solid organs, the transplanted organs are mainly affected. The symptoms of the affected organ are associated with fever of unknown origin and typical for CMV changes in the overall blood picture [43]. In liver transplantation, the differential diagnosis of rejection and CMV hepatitis is difficult [10, 43].

In *HIV-infected persons*, the eyeball tissue is usually the first to be affected. Most often the process is bilateral, especially in the absence of ART, the level of CD4 + is<50 cells / $mm^3$and the immune recovery syndrome develops**.** CMV retinitis does not always begin with scotomas, decreased visual acuity, photophobia, loss of visual field and the appearance of "floating flies" before eyes [28, 35]. Sometimes the symptoms may be absent. But when examining the retinal fundus, the "omelette with ketchup" symptom is always detected [35], which are perivascular yellow-white infiltrates with hemorrhages [28, 35]. When there is immune recovery syndrome, vitreitis may develop, that is, the inflammation of the vitreous body. This syndrome usually manifests 1-3 months after the onset of highly active ART. The reduced visual acuity and vision loss, as complications in these cases, result from cataracts, retinal detachment, cystoid macular edema, or damage to the zone 1 of the cerebral cortex [35]. Colitis occurs in 5-10% of HIV-infected people in AIDS stage. Such symptoms as severe weakness, fever, abdominal pain, profuse diarrhea, weight loss, and anorexia are characteristic. Some complications can occur, such as intestinal hemorrhage and perforation of the intestinal walls. CMV-esophagitis is rare, being accompanied by fever, odynophagia, localized retrosternal pains and nausea [28, 35]. To make the diagnosis of CMV pneumonitis, several criteria must be considered: 1) the presence of interstitial infiltrates in the lungs on a radiograph or CT scan; 2) intracellular inclusions in the lung tissues (typical for CMV); 3) the absence of another pathogen that can cause pneumonitis [35]. The damage to the nervous system is clinically manifested as dementia, myeloradiculitis and ventriculo-encephalitis [28, 35]. At the same time, they are obligate in CSF mononuclear pleocytosis and proteinuria [35]. The association with the following symptoms determines the process nature and localization. The appearance of fever, drowsiness and impaired consciousness indicates the development of dementia. Disturbances of consciousness can result in reduced attention and memory, delirium, spatial and/or temporal disorientation. The appearance of progressive paresis of the lower extremities and dysfunction of the pelvic sphincters subsequently indicates myeloradiculitis. In ventriculoencephalitis, in addition to ataxia, nystagmus, progressive delirium and cranial nerves lesions, MRI revealed signal amplification in the periventricular zone [44].

Laboratory diagnosis

Studies are performed on certain groups of patients: 1) women who are pregnant or who are planning their pregnancy, with the history of miscarriages, congenital malformations and stillbirths; 2) pregnant women diagnosed with hepatitis, hepatosplenomegaly, fever of unknown origin, or detected by ultrasound, symptoms of intrauterine infection; 3) patients with immunodeficient conditions (HIV, cancer, treatment with immunosuppressants, hemodialysis, etc.); 4) children with congenital or acquired CMVI symptoms; 5) all patients with sepsis, meningoencephalitis, severe pneumonia, hepatitis, impairment of the digestive tract and eyes [45, 46, 47]; 6) donor and recipient of blood components, organs, tissues and sperm before each donation; 7) history of sexual contact with a seropositive partner.

Methods of laboratory diagnosis

Virusoscopic method. The main morphological feature, active infection – giant cells with intranuclear and intracytoplasmic inclusions, "cytomegaly." This symptom is found only in 50% of cases.

Virological method. Almost any body fluid or tissue can be cultivated. The culture for the virus should consist of a single layer of human embryonic fibroblasts and a double layer of human lung cells. The cultivation duration is up to 6 weeks.

Serological methods. Their essence is to identify viral antigens (Ag) interacting with each other and antibodies (Ab) produced by the body against them. Enzyme-linked immunosorbent assay (ELISA) is the most common and affordable test. It determines the degree of avidity and the

presence of CMV antibodies of classes IgA, IgM and IgG. (Avidity is the stability of Ag-Ab immunocomplexes, which characterizes the antibodies activity). In 5-7 days, after the initial infection Ab IgM appear in the blood and persist for 1-2 months [44]. After 10-14 days of infection, low-avid IgG appear. Within 1–3 months, high-avid IgG appear and grow, and remain in the blood for the entire life [48]. When the process is reactivated, the hyperproduction of IgA is more typical than IgM. The presence of low avid antibodies indicates a primary infection, and a highly avid infection, a reactivation or latent infection. To establish the process activity, ELISA is repeatedly carried out, in order to determine the follow-up changes in the level of Abs [49]. It is to be noted that this method does not always reflect the real state of the patient. As in the immunodeficiency conditions, the immune system is not able to produce a sufficient amount of antibodies, which can be regarded as a low process activity [30]. If a congenital infection is suspected, antibodies are detected in the blood in the first 3 weeks after birth. Otherwise, Ab can be detected after 3 weeks, as a result of natural feeding with infected CMV milk [13]. Immunofluorescence (IF) reactions are used to establish the infectious process activity. IF is based on the detection of fluorescent Abs. Ab labeled with fluorochrome do not lose the ability to connect with the corresponding Ag and thereby cause a blue-violet glow. The presence of antigen luminescence in the nucleus and cytoplasm of cells reveals pp72 and pp65 proteins [49]. Another method of indirect immunofluorescence is applied after 12-24 hours of cultivation in a test tube, centrifuged and stained with monoclonal CMV-specific antibodies. This method is much more sensitive and accelerates the duration of the study [50, 51]. Also, researchers carry out reactions of binding complement and indirect hemagglutination.

M**olecular biological method** is a specific and highly sensitive study, and it is used as the main method of diagnosing CMVI as an opportunistic infection [52, 53]. The viral DNA genome is determined by the polymerase chain reaction (PCR). It is possible to determine the viral load, which is important in determining the follow-up treatment efficacy. Both latent and active infections are detected. The presence of DNA in the blood and urine indicates a high viral activity, i.e. the presence of CMV, while the DNA presence only in saliva, and indicates an infection [54]. The presence of CMV DNA in the amniotic fluid indicates 100% damage to the fetus [53].

Cytological method – its positive result proves the presence of CMVI in 100%. The virus can be detected in all the body secretions, CSF, urine, tissue biopsies. The staining of biomaterial smears and tissue sections is carried out using dyes (hematoxylin-eosin or Romanovsky-Giemsa). Specific cells, cytomegalovirus, containing large intranuclear and cytoplasmic inclusions, similar to the owl's eye, are identified in various shapes and sizes. They contain a breeding virus inside.

Histological examination is the "gold standard" in obstetrics. The placenta study determined its hyperplasia, cytomegaly, thrombosis and focal ischemic infarctions, fibrinoid necrosis of the chorionic villi stroma and damage to the basal decidual cells [51]. But the method has a number of drawbacks: low sensitivity of intravital diagnosis, that is why, a negative result requires the biomaterial test to be repeated daily for 3-5 days. This study is effective only at the infectious process peak.

Treatment

The treatment method depends on the age, the immune system state and the presence of associated conditions. Currently, only antiviral nucleoside drugs and a specific human anti-cytomegalovirus immunoglobulin have shown their antiviral efficacy in evidence-based medicine. The immunoglobulin containing donor IgM CMV provides passive immunity [54].

The indications for the use of immunoglobulin are prevention in and treatment of: pregnant women with acute CMV infection during the initial infection (IgM and IgG are present in the blood); pregnant women with active CMV infection (detection of CMV DNA, IgM in the blood and urine, CMV DNA in the amniotic fluid); newborns and children under 3 years old, with CMV DNA found in the biomaterial in the first 2 weeks of life; premature or hypotrophic newborns and children under 3 years old with intranatal infections; children with active CMV (CMV DNA in blood); patients before transplantation; recipients in the post-transplantation period [55].

Children under 3 years of age are administered 1 mg / kg once every 48 hours (6 times) [55]. Anti-cytomegalovirus immunoglobulin is intravenously administered 150 mg / kg 72 hours before transplantation and in the next 2, 4, 6, 8 weeks after transplantation, and in 12 and 16 weeks, 50-100 mg [8].

The first-line antiviral drugs include ganciclovir and valganciclovir, the second is foscarnet and cidofovir. Ganciclovir is a synthetic analogue of purine and is converted by phosphotransferase (UL 97) and other enzymes in infected host cells to ganciclovir triphosphate. The latter, in turn, is embedded in the synthesized viral DNA. This leads to the termination of CMV replication. This drug has proven to be highly effective against the rest of herpes viruses. Valganciclovir is ether and a prodrug of ganciclovir. Valganciclovir has an advantage: its oral absorption and bioavailability are the same as the intravenous administration of ganciclovir [56]. The disadvantages of these drugs are: prolonged therapy causes the development of resistance, due to the mutation of UL97 [13, 28], and the suppression of hematopoiesis, especially leukocytes [57]. Ganciclovir is administered intravenously 5 mg / kg every 12 hours for 14-21 days, or 6 mg / kg orally per day for 5 days (+ 100-120 days after the transplant). Valganciclovir, 900 mg per day for 14-21 days. Foscarnet- pyrophosphate compound inhibits herpes virus DNA polymerase. It differs from previous drugs, namely, it does not need phosphorylation for its activity. Also, it inhibits HIV retrotranscriptase. Disadvantages: only endove-

nous route of administration, reduced levels of calcium, magnesium, potassium, blood phosphorus and nephrotoxicity. It is administered 60 mg / kg every 8 hours for 2–3 weeks, afterwards 90–120 mg / kg. Cydofovir is a synthetic nucleoside analogue which stops the synthesis of viral DNA by inhibiting DNA polymerase. It is active not only against herpes viruses, but also human papilloma viruses, pox viruses and adenoviruses. Intravenous administration – 5 mg / kg per week for 2 weeks in a row.

Indications for the administration of antiviral drugs are: treatment of CMV retinitis, prevention of CMV intransplant recipients, prevention of CMVI in HIV-infected people (ganciclovir for adults and children only), treatment of CMV colitis, esophagitis.

Prevention

Non-specific prophylaxis includes public awareness of transmission routes, risks of infection, and consequences for children and immunocompromised people.

Pregnant women should avoid contact with CMV infected children. After the birth of the fetus with CMVI, it is necessary to keep a 2 year pause until the next pregnancy. Measures should be taken to identify seronegative pregnant women and their laboratory monitoring.

The Federal Agency of the USA *Department of Health Centers for Disease Control and Prevention* (CDC) was created in 1946 in the state of Georgia, and its role is to ensure the protection of public health by providing information in order to improve health care solutions. It made recommendations on the need to raise awareness of the population, especially women of childbearing age for the specific prevention of CMV. In 2000 the National Medical Academy of the United States of America published an article about the high priority of developing a vaccine against CMV, which has become a big stimulus for vaccine manufacturers.

At present, still there is no officially specific prevention, but active research is underway to develop a vaccine against CMV. But there are several recombinant CMV vaccines undergoing clinical trials. It was found that women vaccinated with recombinant gB were 50% less likely to become infected compared to women who received placebo [58].

There were identified 4 groups of patients in need of a vaccine against CMV: CMV seronegative and CMV seropositive women of childbearing age, seronegative recipients of solid organs and bone marrow obtained from CMV seropositive donors [59].

Conclusions

1. Cytomegalovirus infection is very common and poses a great danger to people with low immunity and children.

2. The infection frequency indicates a low level of social development of the population.

3. Currently, there is an increase in the infection rate all over the world, which is connected both with the improvement of the diagnosis quality and real disease growth.

4. The study of CMVI characteristics is rapidly developing, although some issues concerning diagnosis, treatment and prevention are still open: expensive diagnosis and treatment, lack of vaccine.

5. According to the CDC recommendations, more extensive public information is needed, especially for young women of childbearing age.

6. It is also necessary to pay great attention to CMV study in the training of doctors in the Republic of Moldova.

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