УДК: 616.34
DOI:10.37800/RM.2.2023.89-98

ON THE CLASSIFICATION OF CYTOMEGALOVIRUS INFECTION IN NEWBORN CHILDREN

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Abstract

Relevance: Cytomegalovirus (CMV) infection is the most common infection that is most commonly found in sick newborns and may be the leading cause of their morbidity and mortality. Current research and clinical observations confirm the likelihood of contracting CMV infection not only in the antenatal period but also in the perinatal and postnatal periods.

The study aimed to comment on the current understanding of neonatal CMV infection, its clinical manifestations depending on the time of infection, perinatal outcomes, and long-term consequences to develop a functional classification of CMV infection in newborns.

Materials and methods: A systematic review and analysis of the literature sources published by scientists in neonatology and perinatology, healthcare practitioners, and professional associations was carried out. Literature searches were conducted in PubMed, Embase, Scopus, and Euro-Peristat over the past decade by the study keywords. A total of 30 sources were included in the analysis.

Results: Delayed sequelae, symptomatic and asymptomatic congenital and perinatal infections have been identified. A review shows that, to date, the incidence of asymptomatic congenital CMV infection has not been established. There is no systematization of the clinical manifestations and outcomes of congenital, perinatal, and postnatal CMV infection in newborns.

Conclusion: Based on the literature review, we have developed a functional classification of CMV infection in newborns by the time of infection. Thus, CMV infection can be congenital, perinatal, or postnatal. The classification presents manifestations of symptomatic forms of CMV infection, perinatal and distant outcomes. However, there are no clear diagnostic criteria for asymptomatic forms of CMV infection. There is no clear rationale for etiopathogenetic therapy, prognostic and preventive criteria for various forms of CMV infection. All of the above tasks require further prospective cohort studies.

Keywords: *newborn, congenital, perinatal, postnatal, cytomegalovirus (CMV) infection.*

Introduction: In recent decades, the problem of congenital and perinatal infections has been widely studied worldwide. The number of cases reaches 65.6% of all causes of perinatal morbidity and 31% of mortality in newborns. The relevance of this problem is due not only to significant peri- and postnatal losses but also to the high risk of disability of such patients. Among congenital and perinatal infections, cytomegalovirus (CMV) infection is the most common, causing manifestations ranging from asymptomatic to severe generalized forms with damage to many organs and systems. Currently, many publications are devoted to modern methods of diagnosing congenital CMV infection, features of clinical manifestations, therapeutic possibilities, prognosis, and long-term outcomes. However, despite many research works in the field of perinatology and neonatology concerning aspects of transmission routes, early detection, and treatment of CMV infection in newborns, questions on approaches to managing infected full-term and premature newborns are still not clarified. Establishing a clinical diagnosis of "congenital and perinatal CMV infection" is a difficult task due to the absence of specific symptoms and polymorphism of clinical symptoms. In addition, to date, there is no accurate data on the incidence of asymptomatic CMV infection.

The study aimed to comment on the current understanding of neonatal CMV infection, its clinical manifestations depending on the time of infection, perinatal outcomes, and long-term consequences to develop a functional classification of CMV infection in newborns.

Materials and Methods: A systematic review in PubMed, Embase, Scopus, and Euro-Peristat databases included literature sources published over the past decade. The search was done by the keywords "cytomegalovirus infection" and "newborn," "congenital, perinatal and postnatal cytomegalovirus infection," "symptomatic, asymptomatic form of CMV infection, «immediate and long-term outcomes," and "classification," including variants of these terms. The terms of medical subject headings (MeSH) were used where possible. The search was limited to data on newborns; the language restrictions were "English" and "Russian." In addition, the search was limited only to full texts of works. Restrictions on the availability of articles were not considered (all sources can be requested from the authors). Case reports, case series, and reviews were excluded. The authors used the "snowball" method when navigating through the links in the studied articles, including reviews, to find additional sources. A total of 33 sources were included in the analysis.

Results: CMV infection etiology

The pathogen belongs to the Cytomegalovirus hominis species, subclass Deoxyvira, class Deoxicubika, order Haplovirales, family Herpesviridae (human herpesvirus type 5), subfamily Betahepresviridae, genus Cytomegalovirus. Four strains of CMV (AD 69, Davis, Towne, Kerr), which are pathogenic to humans, are currently registered.

According to a phylogenetic analysis by Alwan et al., three genotypes of the virus have been identified: gB1, gB2, and gB3 (Figure 1) [1].

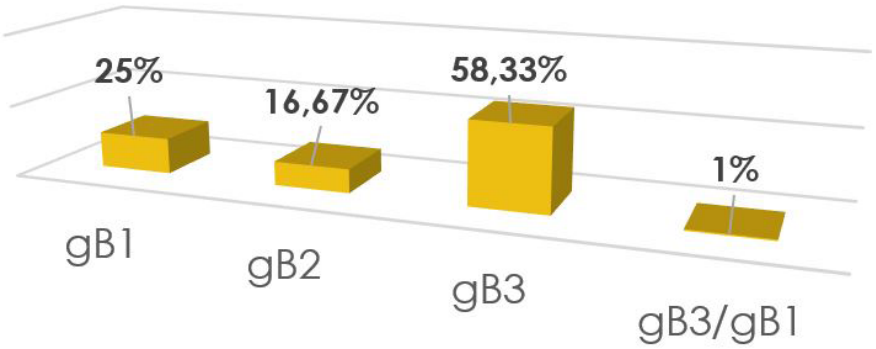

Figure 1 – Cytomegalovirus genotype structure [1]

As can be seen, gB3 human cytomegalovirus was the most frequent genotype detected in 58.33% of infants with symptoms of CMV infection, followed by gB1 (25%) and gB2 (16.67%). However, the gB4 genotype was not detected. Mixed CMV with gB3/gB1 infection was detected in only one case. Thus, gB3 human cytomegalovirus was the most predominant genotype among newborns with symptoms of congenital and perinatal CMV infection [1].

Epidemiology of CMV infection

CMV infection is widespread in all regions of the world (Figure 2).

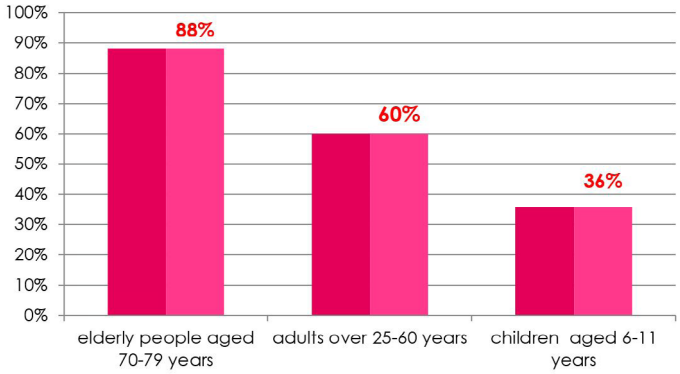

Figure 2 – CMV seropositivity in people of different ages [2]

As shown in the diagram, specific antibodies (CMV seropositivity) are present in 88% of people aged 70-79 years, 60% of adults aged 25-60 years, and 36% of children of 6-11 years [2].

An infected person remains a lifelong virus carrier; most often, the virus remains latent. The higher the population's economic well-being, the higher the average age of contracting CMV and the lower the proportion of infected women of childbearing age (Figure 3) [3]. The chart provides no data on West Europe or the USA.

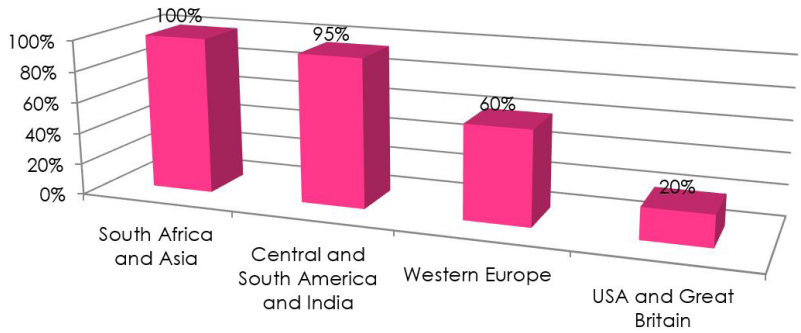

Figure 2 – CMV seropositivity in people of different ages [2]

The percentage of seropositivity of women of childbearing age is: in South Africa and Asia – 100%, in Central and South America and India – 95%, in Western Europe – 60%, in the US and the UK – 20% [3].

The incidence of CMV infection in newborns ranges from 0.2-2.0%. In preterm infants, it is significantly higher and amounts to 16.0-18.0% [4].

Five percent of CMV-infected newborns will have symptoms at birth, including cytomegalic inclusion disease. Complications such as hearing loss and mental retardation

will eventually develop in 15% of cases.

In a systematic review and meta-analysis, including 77 studies from 36 countries with a total of 515,646 newborn children under three weeks, the overall prevalence of congenital CMV infection was 0.67%. Worth noting that the infection rate in low- and middle-income countries was thrice higher than in high-income countries [5].

Thus, the prevalence of CMV infection in populations of different age groups is largely determined by socioeconomic status.

CMV persistence

A special variant of the disease is the latent form of infection, in which the pathogen is defective and maintains its vital activity due to intracellular parasitism without being released into the external environment. After primary and non-primary infection, strains of congenital CMV infection are in a latent state. All herpes viruses ate distinguished by the ability to latency in an infected person's body. For life, the virus is localized in blood lymphocytes, but it can persist in monocytes, polymorphonuclear leukocytes, nerve cells of regional ganglia of sensitive nerves, cells of salivary glands, kidneys, and other organs. Under the influence of certain factors (intercurrent illness, stressful situations, etc.), a latent infection reactivates and transforms into an acute manifestation (manifestation from the Latin manifestatio – detection, manifestation) with the usual properties of the pathogen restored. Conversely, a manifest form may transform into a latent form [6].

CMV infection transmission pathways

An infected person is the only source of infection. The CMV transmission ways are diverse: airborne, contact, sexual, and transplacental (from mother to fetus) during organ transplantation and blood transfusion of an infected donor [3].

Congenital CMV infection

It is an infectious disease resulting from the antenatal transmission of the pathogen from mother to fetus through primary infection of the pregnant woman, reactivation of a previously acquired infection during pregnancy, or infection of a seropositive pregnant woman with another CMV strain [7].

Congenital CMV infection, the most frequent infectious fetopathy, is a pressing problem due to the possibility of a severe generalized process, congenital malformations, and the potential risk of developing chronic pathology [5].

This infection can occur due to primary or non-primary CMV infection in pregnant women. The risk of intrauterine transmission increases when primary infection occurs during pregnancy [8], with a higher rate of vertical transmission in mothers with older gestational age at the time of infection, while the risk of adverse effects on the fetus increases significantly if the infection is contracted during the first half of pregnancy. During pregnancy, reactivation or reinfection of CMV occurs much more often than primary infection with the virus. At that, some studies report that secondary CMV infection causes 50-80% of all cases of intrauterine infection. It has been established that the clinical manifestations and severity of congenital infection depend on the type of pathogen, its virulence, and the level of immunological reactivity of the organism. With antenatal infection, the clinical symptoms of the disease, as a rule, manifest themselves already at birth. At that, with intranatal infection, the clinical manifestation of congenital infection may debut not only in the first weeks of life but also much later, in the post-neonatal period [9].

Congenital CMV infection can cause congenital malformations, ante- or intranatal fetal death, severe generalized disease of the newborn up to death, and irreversible disabling disorders, such as sensorineural hearing loss, blindness, cerebral palsy, neuropsychiatric development delay.

In the study by H. Imafuku et al. (2020), a combination of flu-like symptoms during pregnancy in the mother, fetal ultrasound abnormalities, or premature birth at less than 34 weeks of pregnancy showed a sensitivity of 90.6%, specificity of 66.4%, and a maximum Yuden index of 0.57, and they can be considered as optimal prognostic factors [10].

Infection can affect almost all organs and systems:

- Central nervous system and sensory organs (microcephaly, encephalitis with possible calcification, hearing loss, chorioretinitis, cataract, microphthalmia);
- hepatobiliary system (hepatomegaly, hepatitis, cholangitis, and intrahepatic cholestasis);
- hematopoiesis system (thrombocytopenia, anemia, extramedullary hematopoiesis);
- urinary system (interstitial nephritis);
- respiratory system (pneumonitis);
- gastrointestinal system (esophagitis, gastritis, enterocolitis with ulceration of the mucous membrane)
- endocrine glands (adrenal glands, pancreas, thyroid gland, salivary glands);

According to Alwan et al., jaundice is the most common clinical sign in symptomatically infected newborns, followed by hepatosplenomegaly [1].

Congenital CMV infection is still one of the main causes of hearing loss in the pediatric population, and there is a broad debate about the introduction of universal screening of newborns for CMV infection [11].

With the widespread use of assisted reproductive technologies in obstetrics, publications on perinatal outcomes of pregnancies conceived by in vitro fertilization (IVF) have appeared in the literature.

According to A.A. Permyakova et al., preterm birth occurs in 65.2% of IVF cases. At that, the infection rate of CMV infection in PCR samples of saliva and urine in this group of premature babies in the first year of life is 21%. According to the authors, the high prevalence of herpes virus infection in children born through IVF dictates the need for a non-invasive screening PCR study of saliva and urine to identify CMV DNA and determine the viral load [12].

Thus, congenital CMV infection is a highly prevalent, adverse neonatal disease. Joint activity of obstetrician-gynecologists, infectious disease specialists, and neonatologists is required to improve the perinatal outcomes of CMV infection.

Perinatal and postnatal CMVI infection

Perinatal CMV infection in term infants is often asymptomatic. Extremely rarely manifests as CMV enterocolitis with a clinic of watery diarrhea complicated by exsiccosis, hemocolitis, stenosis, or intestine perforation [11]. Postnatal infection through breast milk is discussed since PCR detects CMV DNA in the mother's milk. At that, it is not found in dry spots of the child's blood (on Guthrie's map) [3].

Iwanaga et al. describe the manifestation of severe enterocolitis in a girl of 6 weeks on mixed feeding. She developed watery diarrhea with a loss of protein, exsiccosis, hypoproteinemia (30 g/L), hypoalbuminemia (17 g /L), a marked increase in ALT (581 units/L) and AST (280 units/L) levels, and anemia [18].

Sue et al. describe a severe course of MV enterocolitis in 2 children, eight weeks and ten months old. Histological examination revealed pronounced destruction of crypts, inflammatory infiltration, and immunohistochemically – multiple CMV inclusions. CMV DNA was detected in blood plasma by PCR. The child received four weeks of parenteral antiviral treatment (ganciclovir) and valganciclovir orally for the next four weeks [13].

CMV infection can cause severe enterocolitis postnatally and in the first months of life, aggravating the course of necrotizing enterocolitis (NEC). Vajnshtejn and co-authors presented cases of CMV enterocolitis and NEC. Two full-term infants developed severe watery diarrhea, and one had blood in the feces. A premature newborn with CMV infection had a worsening of the NEC course. Those patients received ganciclovir and specific intravenous immunoglobulin with a favorable outcome [3].

In Minihan et al. studies, 48 CMV-positive newborns were identified out of 1,659 newborns (average gestational age 25.3 weeks, birth weight 695 g, age 58 days) (frequency of 2.9%). The most common symptoms were bloating (43.8%), sepsis-like syndrome (29.2%), thrombocytopenia (60.5%), and conjugated hyperbilirubinemia (60.9%). Compared with the controls, there was no significant difference in the combined number of fatal cases or bronchopulmonary dysplasia (56.3% vs. 37.5%; P = 0.1) or neurodevelopmental disorders after 1 and 2 years (51.9% vs. 44%; P = 0.8; 71.4% vs 50%; P = 0.4) [14].

According to Mukhopadhyay et al., symptomatic postnatal CMV infection has been diagnosed in 1.3% of extremely low and very low birth weight children, most commonly among those weighing less than 1000 grams with respiratory instability and thrombocytopenia littoralis. The authors summarized that, like late-onset bacterial infection, symptomatic postnatal CMV infection may contribute independently to the development of bronchopulmonary dysplasia. This possibility should be considered in a prospective study of newborns with extremely low body weight [15].

Restrepo-Gualteras and others claim that CMV infections of the respiratory system are more common in premature newborns. At the pulmonary level, active CMV infection is usually characterized by an alveolar disorder leading to hypoxemia, opaque glass-type darkening, and interalveolar infiltrates with CMV inclusions, according to lung biopsy. The detection of active CMV infection in the respiratory tract organs is accompanied by an additional assessment of immune defects (primary or secondary) that disrupt the function of T and NK cells or the innate antiviral response, as well as other changes in immune regulation. General clinical and radiological patterns, such as hypoxemia and pulmonary darkening by the type of frosted glass, make it possible to detect CMV infection of the respiratory organs in the early stages and begin specific treatment of the liver [16].

Acquired CMV infection should be suspected in children with very low and extremely low body weight, breastfed by seropositive mothers, and showing severe symptoms, especially sepsis with negative cultures [17]. This may allow pediatricians to make better diagnoses, conduct supportive therapy, provide antiviral treatment if necessary, or establish "preventive" therapy for these high-risk newborns.

In the research by Weimer et al., postnatal CMVI infection is associated with long-term consequences for the hearing and growth of children with extremely low and very low body weight and prolonged hospitalization. Prospective studies are needed to determine all the consequences of postnatal CMV infection and the effectiveness of antiviral treatment [18].

Thus, a high-risk group for developing perinatal and postnatal CMV infection comprises deeply premature infants who do not have passively acquired maternal antibodies, contributing to their morbidity and mortality [19].

CMV infection of the fetus and newborn: detection by laboratory diagnostic methods

Indirect diagnostic methods and serological studies are the main tools for assessing CMV infection during pregnancy. CMV-specific class M antibodies (IgM) have been used as a diagnostic marker of primary CMV infection in pregnant women, although CMV-IgM has been detected in non-primary CMV infections. According to a systematic review by Iijima, IgG avidity testing can help distinguish primary CMV infection from non-primary; however, there is no standardized analysis to detect this difference. Besides, when the mother is positive for CMV-IgG and negative for specific IgM, the probability of vertical transmission after primary CMV infection is often excluded. However, symptomatic congenital CMV infections have recently been reported regarding negative outcomes for maternal CMV-IgM [20]. The absence of CMV-IgM occurred in both primary and non-primary CMV infections. In addition, non-primary CMV infections in the mother during pregnancy may lead to a greater proportion of symptomatic congenital CMV infections than previously thought. If universal prenatal screening is performed, an ultrasound examination to detect fetal abnormalities should be performed regardless of the presence of antibodies to CMV-IgM in a pregnant woman. Screening for CMV antibodies should be performed whenever routine fetal ultrasound reveals abnormality [20].

If a CMV infection of the fetus is suspected, an examination of the amniotic fluid or urine of newborns for DNCCMV is required. The gold standard for diagnosing congenital CMV infection is an invasive procedure called amniocentesis. Tanimura & Yamada found that the presence of CMV DNA in the secretion of the mother's cervix is a prognostic criterion for congenital CMV infection in pregnant women with anti-CMV IgM-emia. According to the authors, maternal serological screening for primary CMV infection does not always allow for diagnosing newborns with congenital CMV infection. This screening detects CMV-specific immunoglobulins G, avidity index IgG, or specific IgM. In this regard, scientists suggest identifying potential biomarkers for predicting congenital CMV infection [8].

The IgG or specific IgM AVIDITY index misses several newborns with congenital CMV infection. Scientists suggest finding potential biomarkers for predicting congenital CMV infection [21].

Congenital CMV infection in a newborn is diagnosed in the presence of a clinical and laboratory picture before the 21st day of life. The laboratory diagnostics of CMV is based on detecting CMV-infected cells, the virus itself or its DNA, antigens, and specific antibodies to the virus in the studied samples [1]. The polymerase chain reaction method, which combines high sensitivity and specificity, allows the detection of viral DNA directly in the samples under study. The advantage of the method is the possibility of early detection of the pathogen in the patient's body; even an immune response is formed [33].

Saliva PCR seems to be the optimal method of screening newborns for CMV [4]. Some authors report the possibility of using PCR as a screening method for detecting CMV in newborns' saliva and urine [12].

According to H. Imafuku et al. (2020), tests for CMV DNA in the urine of newborns born to mothers with clinical manifestations (age < 25 years: OR – 2.7, 95%, CI 1.1-6.6, p < 0.05; presence of fever in the mother or flu-like symptoms: OR – 5.4, CI 2.6-11.2, p < 0.01; ultrasound abnormalities of fetal development: OR – 12.7, CI 5.8-27.7, p < 0.01; premature birth at less than 34 weeks of gestation: OR – 2.6, CI 1.1-6.0, p < 0.05) can be an effective method of detecting CMV as a targeted screening with high sensitivity [22].

P. Ssentongo et al. reported lower rates in screening methods using blood compared to urine or saliva [5].

Thus, the PCR method of saliva and urine samples in newborns has advantages as a non-invasive diagnostic method and is of diagnostic value in neonatology, especially in premature infants with extremely low and very low body weight.

CMV infection treatment in newborns

CMV is the most common pathogen causing congenital infection and can lead to significant adverse consequences for the development of the nervous system. For this reason, in many regions, the standard of treatment for congenital CMV infection is a six-week course of ganciclovir [21].

Currently, there is no evidence of the benefit of antiviral therapy in asymptomatic children. In case of symptomatic CMV infection, oral treatment with valganciclovir for 12 months is recommended [22]. This therapy has proven effective and tolerable for hearing and neurodevelopment in the long term. Valganciclovir is intended for newborns with disease symptoms at birth, such as microcephaly, intracranial calcifications, chorioretinitis, or sensorineural hearing loss. A multicenter study was conducted with a group of CMV-infected newborns for specific treatment with valganciclovir. The data obtained showed the efficacy and safety of oral treatment with valganciclovir, which allowed this drug to be approved as a treatment for infants with congenital CMV pathology by Japan's state health insurance system [23].

Treatment with antiviral drugs is usually not recommended for newborns with mild symptoms of the disease at birth or newborns under the age of 32 weeks of gestational age link. However, since these populations comprise the vast majority of newborns and infants with CMV infection, they are at risk of developing late complications. In this regard, it is necessary to study biomarkers capable of predicting long-term consequences to justify the initiation of treatment and reduce the percentage of complications associated with CMV.

The literature describes cases of neonatal cholestasis with positive dynamics from antiviral therapy with ganciclovir [24]. And published data on the use of high doses of valganciclovir to prevent congenital CMV infection in pregnant women with primary CMV infection in the first trimester [25].

According to the literature, ganciclovir, and valganciclovir improve long-term audiological and neurological outcomes in patients with CMV infection. However, resistance to antiviral drugs has been documented in some studies link. Thus, Japanese researchers with their co-authors (2022) have identified resistance to antiviral drugs in patients with CMV receiving long-term therapy (for six months). Full-size analysis of UL97 and UL54 using long sequencing made it possible to quickly and comprehensively detect drug resistance mutations [26]. The literature discusses the treatment of CMV with Cyclosporine A, which performs a dual function in the pathogenesis of CMV. It has an immunosuppressive effect that promotes virus replication by inhibiting T-cell function and an anti-CMV effect mediated by early intermediate protein 2 [27].

Thus, the problem of inpatient and outpatient treatment of CMV infection in premature babies remains relevant. The effectiveness of treatment in these patients to prevent further complications was not monitored.

Long-term consequences of CMV infection in children

Recently, progress has been made in the field of congenital CMV infection associated with the antiviral treatment of pregnant women and infants, the introduction of newborn screening programs for CMV, and the frequency and diagnosis of complications among infected children. Today, perinatal CMV infection is increasingly recognized as a potential cause of long-term consequences in addition to acute complications in premature infants, which raises important issues related to treatment and prevention. A study of children who did not undergo newborn hearing screening revealed a higher level (16%) of hearing impairment in the group with the perinatal CMV infection compared to 9% in the control group [28].

New studies show a high incidence of vestibular dysfunction and neuropsychiatric disorders in children with CMV [28]. Some studies report an association between postnatal CMV infection and long-term consequences, including delayed development of the nervous system and bronchopulmonary dysplasia among newborns with very low birth weight. [18] The above was the motivation for strengthening research on the elimination of the virus from breast milk using various methods [29]. To study more distant complications of CMV, previously considered asymptomatic.

Thus, CMV, first of all, negatively affects the child's hearing and contributes to neurological complications, especially in its asymptomatic forms, which requires strengthening monitoring of these children by pediatrist, neurologist, surdologist, and ophthalmologist.

Prevention of congenital CMV infection

Non-randomized studies confirm the potential of CMV hyper immunoglobulin in preventing CMV transmission from mother to fetus, but prospective interventional studies show questionable results. Thus, in a randomized study by R. Devliegera et al. [30], there were no statistically significant differences in CMV infection of the fetus and newborn between a group of pregnant women (average gestational

age 24-25 weeks) treated with intravenous immunoglobulin during pregnancy and a group of mothers who did not receive immunotherapy. The incidence of congenital CMV infection was 13/28 newborns (46.4%; CI 27.51; 66.13) versus 16/45 newborns (35.6% [CI 21.87; 51.22]) in the control and main (treated) groups, respectively (p = 0.46). Neonatal CMV disease was predominantly mild and resolved spontaneously without major safety concerns. [31].

Regarding vaccination against CMV infection, G. Gerna et al. (2020) noted that future efforts are required to confirm if the new recombinant gB vaccine serves better to prevent both primary and non-primary infections [31].

Conclusion: Based on the review of literature sources on the problem of CMV infection in neonatology, we present the functional classification of CMV infection in newborns developed by us (Table 1).

Table 1 – Functional classification of CMV infection in newborns

<table>
<tr><th colspan="4">Types of CMV Infection in Newborns</th></tr>
<tr><td colspan="2">I. Congenital CMV infection
II. Perinatal CMV (pCMV) infection</td><td>II. Perinatal CMVI (CMV) infection</td><td>III. Postnatal
CMV (post-CMV) infection</td></tr>
<tr><td colspan="2">Transmitted by the transplacental route</td><td>Transmitted through the birth canal of the mother</td><td>Through breast milk, transfusion of blood products after birth</td></tr>
<tr><td colspan="2">Asymptomatic form</td><td colspan="2">Manifestations</td></tr>
<tr><td>Heavy and medium-heavy</td><td>• early manifestation
• multiple organ pathology
• hemorrhagic rash in the form of petechiae and purpura (75%)
• jaundice syndrome (63%)
• activation of extramedullary hematopoiesis in the form of a blueberry Muffin (Fig. 1)
• prematurity of intrauterine growth retardation
• high rates of hyperbilirubinemia and increased levels of transaminases
• unexplained thrombocytopenia, leukopenia, anemia</td><td>• deterioration of the general condition
• sepsis-like syndrome
• prolonged jaundice without obvious causes
• pneumonia
• hepatosplenomegaly
• hepatitis
• thrombocytopenia
• hemorrhagic rash</td><td>more often in children with extremely low body weight, very low body weight
• sepsis
• necrotizing enterocolitis with negative cultures and surgical complications (perforation, stenosis, etc.)
• pneumonia with the development of bronchopulmonary dysplasia
• prolonged jaundice without obvious reasons
• enlargement of the liver, spleen
• hemorrhagic rash, etc.</td></tr>
<tr><td>Easy</td><td>• isolated lesion of one or two organs
• clinically insignificant or transient (unexpressed hepatomegaly, splenomegaly)
• single changes – thrombocytopenia, increased hepatic transaminases (ALT, AST).</td><td></td><td></td></tr>
<tr><td>Isolated bathroom hearing loss</td><td>there are no clinical and laboratory signs of the disease except for isolated hearing loss</td><td></td><td></td></tr>
<tr><td colspan="4">Asymptomatic form</td></tr>
<tr><td colspan="4">• CMV + in blood, urine, saliva
• there are no clinically significant signs of the disease
• hemogram and biochemical blood test – no changes
• instrumental examinations – no changes
!!! During the first 3-6 months of life, delayed psychomotor development, sensorineural hearing loss, and chorioretinitis (“late” manifestations of congenital CMV infection) gradually begin to form.</td></tr>
<tr><td colspan="4">Complications – long-term outcomes</td></tr>
<tr><td colspan="4">• - central nervous system damage - neurological dysfunctions, motor disorders, hearing and vision loss, decreased learning ability, speech defect, etc.
• - the defeat of the hepatobiliary system – biliary cirrhosis (hepatitis, biliary tract infection)
• - cardiomyopathy, arrhythmias</td></tr>
</table>

It follows from the presented classification that both symptomatic and asymptomatic forms of congenital, perinatal, and postnatal CMV infection may have delayed complications, primarily from the nervous system and sensory organs, which requires constant clinical and laboratory monitoring of CMV infection in children in the post-neonatal period, especially during early development.

It should be noted that there is insufficient data today, and clear diagnostic criteria for asymptomatic forms of CMV infection have not been established. The latter manifest at different ages; in this regard, it is important to develop criteria for the prognosis and prevention of various forms of CMV infection.

Although the serological criteria for diagnosing primary CMV infection are well known, the criteria for diagnosing non-primary infection are still incomplete. There is a need for clear clinical and laboratory justifications for conducting one or another etiopathogenetic therapy. The problem of treating CMV infection is aggravated by CMV strains resistant to ganciclovir. Therefore, optimizing treatment regimens in children with CMV infection continues and remains an urgent problem. The issues of their further dispensary observation have not been fully resolved.

There is still debate about whether human hyperimmune globulin is capable of protecting against vertical transmission of CMV. In conclusion, it should be noted that developing a CMV vaccine that will prevent a significant part of congenital CMV infection will be an important progressive step in the development of vaccination and prevention of both primary and non-primary infections during pregnancy.

СПИСОК ЛИТЕРАТУРЫ:

1. Alwan S.N., Shamran H.A., Ghaib A.H., Kadhim H.S., Al-Mayah Q.S., AL-Saffar A.J., Bayati A.H, Arif H.S., Fu J., Wickes B.L. Genotyping of Cytomegalovirus from Symptomatic Infected Neonates in Iraq // Am. J. Tropic. Med. Hygiene. – 2019. – Vol. 100(4). – P. 957-963. https://doi.org/10.4269/ajtmh.18-0152
2. Staras S.A.S., Dollard S.C., Radford K.W., Flanders W.D., Pass R.F., Cannon M.J. Seroprevalence of Cytomegalovirus Infection in the United States, 1988-1994 // Clin. Infect. Dis. – 2006. – Vol. 43(9). – P. 1143-1151. https://doi.org/10.1086/508173
3. Вайнштейн Н.П., Британишская Е.А., Митина Ю.Ю., Матвеева Т.В., Саркисян Е.А. Роль цитомегаловирусной инфекции в поражении желудочно-кишечного тракта у новорожденных и детей раннего возраста / // Неонатология: новости, мнения, обучение. – 2018. – Т. 6, № 4(22). – С. 70-85 [Vajnshtejn N.P., Britanishskaya E.A., Mitina Yu.Yu., Matveeva T.V., Sarkisyan E.A. Rol' citomegalovirusnoj infekcii v porazhenii zheludochno-kishechnogo trakta u novorozhdennyx i detej rannego vozrasta / // Neonatologiya: novosti, mneniya, obuchenie. – 2018. – T. 6, № 4(22). – S. 70-85 (in Russ. https://www.elibrary.ru/item.asp?id=36510728
4. Yamada H., Tanimura K., Fukushima S., Fujioka K., Deguchi M., Sasagawa Y.., Tairaku S, Funakoshi T., Morioka I. A cohort study of the universal neonatal urine screening for congenital cytomegalovirus infection // J. Infect. Chemother. – 2020. – Vol. 26(8). – P. 790-794. https://doi.org/10.1016/j.jiac.2020.03.009
5. Ssentongo P., Hehnly C., Birungi P., Roach M.A., Spady J., Fronterre C.., Wang M., Murray-Kolb L.E., Shaar L.A., Chinchilli V.M., Broach J.R., Ericson J.E., Schiff S.J,. Congenital Cytomegalovirus Infection Burden and Epidemiologic Risk Factors in Countries With Universal Screening: A Systematic Review and Meta-analysis // JAMA Netw Open. –2021. – Vol. 4(8). – Art. no. e2120736. https://doi.org/10.1001/jamanetworkopen.2021.20736
6. Баранова И.П., Карнеева Ж.Н., Коннова О.А. О рабочей классификации и структуре диагноза цитомегаловирусной инфекции у детей раннего возраста // Инфекц. болезни: новости, мнения, обучение. – 2016. – № 3(16). – С. 42-48 [Baranova I.P., Karneeva Zh.N., Konnova O.A. O rabochej klassifikacii i strukture diagnoza citomegalovirusnoj infekcii u detej rannego vozrasta // Infekc. bolezni: novosti, mneniya, obuchenie. – 2016. – № 3(16). – S. 42-48 (in Russ.)]. https://www.elibrary.ru/item.asp?id=26637770
7. Ross A.S., Fowler B.K., Ashrith G., Stagno S., Britt W.J., Pass R.F., Boppana S.B., Hearing loss in children with congenital cytomegalovirus infection born to mothers with preexisting immunity // J. Pediatr. – 2006. – Vol. 148(3). – Art. no. 332. https://doi.org/10.1016/j.jpeds.2005.09.003
8. Tanimura K., Yamada H. Maternal and neonatal screening methods for congenital cytomegalovirus infection // J. Obstet. Gynaecol. Res. – 2018. – Vol. 27(12). – Art. no. 12. https://doi.org/10.1111/jog.13889
9. Шкарин В.В., Послова Л.Ю., Ковалишена О.В., Сергеева А.В., Сенягина Н.Е. Эпидемиология внутриутробных и внутрибольничных инфекций новорожденных: учебное пособие. — Н. Новгород: Изд-во «Ремедиум Приволжье», 2019. — 124 с. [Shkarin V.V., Poslova L.Yu., Kovalishena O.V., Sergeeva A.V., Senyagina N.E. E'pidemiologiya vnutriutrobnyx i vnutribol'nichnyx infekcij novorozhdennyx: uchebnoe posobie. — N. Novgorod: Izd-vo «Remedium Privolzh'e», 2019. — 124 s. (in Russ.)]. https://doi.org/10.21145/978-5-906125-71-2_2019
10. Imafuku H., Yamada H., Uchida A., Deguchi M., Shirakawa T., Sasagawa Y., Shi Y., Fujioka K., Morioka I., Tanimura K. Clinical and ultrasound features associated with congenital cytomegalovirus infection as potential predictors for targeted newborn screening in high-risk pregnancies // Sci. Rep. – 2020. – Vol. 10(1). – Art. no. 19706. https://doi.org/10.1038/s41598-020-76772-1
11. Palma S., Roversi M.F., Bettini M., Mazzoni S., Pietrosemoli P., Lucaccioni L., Berardi A., Genovese E. Hearing loss in children with congenital cytomegalovirus infection: an 11-year retrospective study based on laboratory database of a tertiary paediatric hospital // Acta Otorhinolaryngol. Italica. – 2019. – Vol. 39(1). – P. 40-45. https://doi.org/10.14639/0392-100X-2020

12. Пермякова А.В., Львова И.И., Махмудова С.Э. Частота выявления цитомегаловирусной инфекции у детей, родившихся в результате применения вспомогательных репродуктивных технологий // Перм. Мед. Ж. – 2017. – Т. 34, № 2. – С. 51-55 [Permyakova A.V., L'vova I.I., Maxmudova S.E'. Chastota vyyavleniya citomegalovirusnoj infekcii u detej, rodivshixsya v rezul'tate primeneniya vspomogatel'nyx reproduktivnyx texnologij // Perm. Med. Zh. – 2017. – T. 34, № 2. – S. 51-55 (in Russ.)]. https://www.elibrary.ru/item.asp?id=29043823
13. Marsico C., Aban I., Kuo H., James S.H., Sanchez P.J., Ahmed A., Boger R.A., Michaels M.G., Ashouri N., Englund J.A., Estrada B., Jacobs R.F., Romero J.R., Sood S.K., Whitworth S., Jester M.P., Whitley R.J., Kimberlin D.W. Collaborative Antiviral Study Group (CAGS). Blood Viral Load in Symptomatic Congenital Cytomegalovirus Infection // J. Infect. Dis. – 2019. – Vol. 219(9). – P. 1398-1406. https://doi.org/10.1093/infdis/jiy695
14. Minihan L., Lee Oei J., Bajuk B., Palasanthiran P. Postnatal Cytomegalovirus Infection: Is it Important? A 10-Year Retrospective Case-control Study of Characteristics and Outcomes in Very Preterm and Very Low Birth Weight Infants // Pediatr. Infect. Dis. J. – 2022. – Vol. 41(7). – P. 579-586. https://doi.org/10.1097/INF.0000000000003531
15. Mukhopadhyay S., Meyer S., Permar S., Puopolo K. Symptomatic Postnatal Cytomegalovirus Testing among Very Low-Birth-Weight Infants: Indications and Outcomes // Amer. J. Perinatol. – 2016. – Vol. 33(09). – P. 894-902. https://doi.org/10.1055/s-0036-1581080
16. Restrepo-Gualteros S.M., Gutierrez M.J., Villamil-Osorio M., Arroyo M.A., Nino G. Challenges and Clinical Implications of the Diagnosis of Cytomegalovirus Lung Infection in Children // Curr. Infect. Dis. Rep. – 2019. – Vol. 21(7). – Art. no. 24. https://doi.org/10.1007/s11908-019-0681-x
17. Garofoli F., Civardi E., Zanette S., Angelini M., Perotti G., Zecca M., Lombardi G., Literature Review and an Italian Hospital Experience about Postnatal CMV Infection Acquired by Breastfeeding in Very Low and/or Extremely Low Birth Weight Infants // Nutrients J. – 2021. – Vol. 13(2). – Art. no. 660. https://doi.org/10.3390/nu13020660
18. Weimer K.E.D., Kelly M.S., Permar S.R., Clark R.H., Greenberg R.G. Association of Adverse Hearing, Growth, and Discharge Age Outcomes With Postnatal Cytomegalovirus Infection in Infants With Very Low Birth Weight // JAMA Pediatr. – 2020. – Vol. 174(2). – P. 133-140. https://doi.org/10.1001/jamapediatrics.2019.4532
19. Lanzieri T.M., Dollard Sh.C., Josephson C.D., Schmid D.S., Bialek S.R. Breast Milk–Acquired Cytomegalovirus Infection and Disease in VLBW and Premature Infants // Pediatrics. – 2013. – Vol. 131(6). – P. e1937-e1945. https://doi.org/10.1542/peds.2013-0076
20. Iijima S. Pitfalls in the Serological Evaluation of Maternal Cytomegalovirus Infection as a Potential Cause of Fetal and Neonatal Involvements: A Narrative Literature Review // J. Clin. Med. – 2022. – Vol. 11(17). – Art. no. 5006. https://doi.org/10.3390/jcm11175006
21. El-Sayed M.F., Goldfarb D.M., Fulford M., Pernica J.M. Severe late-onset multisystem cytomegalovirus infection in a premature neonate previously treated for congenital infection // BMC Pediatr. – 2013. – Vol. 13. – Art. no. 142. http://www.biomedcentral.com/1471-2431/13/142
22. Chiopris G., Veronese P., Cusenza F., Procaccianti M., Perrone S., Daccò V., Colombo C.., Esposito S., Congenital Cytomegalovirus Infection: Update on Diagnosis and Treatment // Microorganizms J. – 2020. – Vol. 8(10). – Art. no. 1516. https://doi.org/10.3390/microorganisms8101516
23. Morioka I., Kakei Y., Omori T., Nozu K., Fujioka K., Yoshikawa T., Moriuchi H., Oka A. Efficacy and safety of valganciclovir in patients with symptomatic congenital cytomegalovirus disease: Study Protocol Clinical Trial (SPIRIT Compliant) // Medicine. – 2020. – Vol. 99(17). – Art.no. 19765. https://doi.org/10.1097/MD.0000000000019765
24. Abolurin O.O., Senbanjo I.O., Adekoya A.O., Ajibola E.D. Congenital cytomegalovirus infection as an important cause of infantile cholestatic jaundice: a case report // Pan Afr. Med. J. – 2020. – Vol. 36. – Art. no. 106. https://doi.org/10.11604/pamj.2020.36.106.20577
25. Shahar-Nissan K., Pardo J., Peled O., Krause I., Bilavsky E., Wiznitzer A., Hadar E., Amir J. Valaciclovir to prevent vertical transmission of cytomegalovirus after primary maternal infection during pregnancy: a randomized, double-blind, placebo-controlled trial // Lancet. – 2020. – Vol. 396(10253). – P. 779-785. https://doi.org/10.1016/S0140-6736(20)31868-7
26. Torii Y., Horiba K., Kawada J ichi., Haruta K., Yamaguchi M., Suzuki T., Uryu H., Kashiwa N., Goishi K., Ogi T., Ito Y. Detection of antiviral drug resistance in patients with congenital cytomegalovirus infection using long-read sequencing: a retrospective observational study // BMC Infect. Dis. – 2022. – Vol. 22. – Art. no. 568 https://doi.org/10.1186/s12879-022-07537-6
27. Abdullah A., Abdullah R., A Nazariah Z., Balakrishnan K., Firdaus J. Abdullah F., A Bala J., Mohd-Lila M.A. Cyclophilin A as a target in the treatment of cytomegalovirus infections // Antivir. Chem. Chemother. – 2018. – Vol. 26. – Art. no. 2040206618811413. https://doi.org/10.1177/2040206618811413
28. Shears A., Yan G., Mortimer H., Cross E., Sapuan S., Kadambari S., Luck S., Heath P.T., Walter S., Fidler K.J., Vestibular and balance dysfunction in children with congenital CMV: a systematic review // Arch. Dis. Child. Fetal. Neonatal Ed. – 2022. – Vol. 107(6). – P. 630-636. https://doi.org/10.1136/archdischild-2021-323380
29. Davis N.L, Miller W.C, Hudgens MG, Chasela CS, Sichali D, Kayira D, Nelson Julie A.E., Fiscus S.A., Tegha G., Kamwendo D.D., Rigdon J., Stringer Jeffrey S.A., Juliano J.J., Ellington S.R., Kourtis A.P., Jamieson D.J., Van Der Horst C.; for the BAN study team. Maternal and Breastmilk Viral Load: Impacts of Adherence on Peripartum HIV Infections Averted—the Breastfeeding, Antiretrovirals, and Nutrition Study // JAIDS. – 2016. – Vol. 73(5). – P. 572-580. https://doi.org/10.1097/QAI.0000000000001145

30. Devliegera R., , Buxmann H., Nigro G., Enders M., Jückstocke J., Siklós P., Wartenberg-Demand A.,Schuttrumpf J., Schutze J., Rippel N., Herbold M., Niemann G., Friese K. Serial Monitoring and Hyperimmunoglobulin versus Standard of Care to Prevent Congenital Cytomegalovirus infection: A phase III Randomized Trial // Fetal Diagn. Ther. – 2021. – Vol. 48. – P. 611-623. https://doi.org/10.1159/000518508
31. Gerna G., Fornara C., Furione M., Lilleri D. Congenital Human Cytomegalovirus Infection: A Narrative Review of Maternal Immune Response and Diagnosis in View of the Development of a Vaccine and Prevention of Primary and Non-Primary Infections in Pregnancy // Microorganisms. – 2021. – Vol. 9(8). – Art. no. 1749. https://doi.org/10.3390/microorganisms9081749

К ВОПРОСУ О КЛАССИФИКАЦИИ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИИ У НОВОРОЖДЕННЫХ ДЕТЕЙ

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Актуальность: Цитомегаловирусная инфекция (ЦМВ) является наиболее распространенной инфекцией, которая чаще всего встречается у больных новорожденных и может быть основной причиной их заболеваемости и смертности. Современные исследования и клинические наблюдения подтверждают вероятность инфицирования цитомегаловирусной инфекцией, не только в антенатальном периоде, но и в перинатальном и послеродовом периодах.

Цель исследования – прокомментировать современные представления о неонатальной цитомегаловирусной инфекции, ее клинических проявлениях в зависимости от времени инфицирования, перинатальных исходов и отдаленных последствий для разработки рабочей классификации ЦМВ-инфекции у новорожденных.

Материалы и методы: Проведен систематический обзор и анализ литературных источников, опубликованных учеными в области неонатологии и перинатологии, специалистами практического здравоохранения и профессиональными ассоциациями. Поиск литературы проводился в базах PubMed, Embase, Scopus, Europeristat за последние 10 лет с использованием ключевых слов исследования. В анализ было включено в общей сложности 30 источников.

Результаты: Выявлены отсроченные последствия, не только симптоматические, но и бессимптомные врожденные перинатальных инфекций. Обзор показывает, что на сегодняшний день частота бессимптомной врожденной ЦМВ-инфекции не установлена. Систематизация клинических проявлений и исходов врожденной, перинатальной и постнатальной ЦМВ-инфекции у новорожденных отсутствует.

Заключение: Основываясь на проведенный обзор литературы, нами разработана рабочая классификация ЦМВ-инфекции у новорожденных детей, которая, в зависимости от времени заражения, может быть врожденной, перинатальной и послеродовой. В классификации представлены проявления симптоматических форм ЦМВ-инфекции, перинатальные и отдаленные исходы. Однако четких диагностических критериев для бессимптомных форм ЦМВ-инфекции не существует. Отсутствуют четкие обоснования для проведения этиопатогенетической терапии, прогностических и профилактических критериев для различных форм ЦМВ-инфекции.

Все вышеперечисленные задачи требуют дальнейших проспективных когортных исследований.

Ключевые слова: *новорожденный, врожденная, перинатальная, постнатальная цитомегаловирусная инфекция, симптоматическая, бессимптомная форма, классификация*

ЖАҢА ТУЫЛҒАН НӘРЕСТЕЛЕРДЕГІ ЦИТОМЕГАЛОВИРУСТЫ ИНФЕКЦИЯНЫҢ ЖІКТЕЛУІ ТУРАЛЫ СҰРАҚҚА

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Тұжырым

Өзектілігі: Цитомегаловирус инфекциясы (ЦМВ) ең көп таралған инфекция болып табылады, ол көбінесе науқас жаңа туған нәрестелерде анықталады және олардың аурушаңдығы мен өлімінің негізгі себебі болуы мүмкін. Заманауи зерттеулер мен клиникалық бақылаулар цитомегаловирусты инфекцияны тек антенатальды емес, сонымен қатар перинаталды, сондай-ақ босанғаннан кейінгі кезеңде де жұқтыру ықтималдығын растайды.

Зерттеудің мақсаты – неонатальды цитомегаловирусты инфекцияның қазіргі түсінігіне, оның инфекция уақытына байланысты клиникалық көріністеріне, перинаталдық нәтижелерге және жаңа туған нәрестелердегі ЦМВ инфекциясының жұмыс классификациясын әзірлеу үшін ұзақ мерзімді салдарға түсініктеме беру болды.

Материалдар мен Әдістері: Неонатология және перинатология саласындағы ғалымдар, медицина қызметкерлері және кәсіптік бірлестіктер шығарған әдебиет көздеріне жүйелі шолу және талдау жүргізілді. Соңғы 10 жыл ішінде зерттеу кілтті сөздері арқылы PubMed, Embase, Scopus, Euro-Peristat сайттарында әдебиеттерді іздеу жүргізілді. Талдауға барлығы 33 дереккөз енгізілді.

Нәтижелері: Тек симптоматикалық ғана емес, сонымен қатар симптомсыз туа біткен, перинаталдық инфекциялардың кешіктірілген салдары анықталды. Шолу бүгінгі күнге дейін симптомсыз туа біткен ЦМВ инфекциясының жиілігі анықталмағанын көрсетеді. Жаңа туған нәрестелердегі туа біткен, перинаталдық және постнатальды ЦМВ инфекциясының клиникалық көріністері мен нәтижелерін жүйелеу жоқ.

Қорытынды: Әдебиеттердегі шолуға сүйене отырып, біз жаңа туған балалардағы ЦМВ инфекциясының классификациясын жасадық, ол жұқтыру уақытына байланысты туа біткен, перинаталды және постнатальды болуы мүмкін. Классификация ЦМВ инфекциясының симптоматикалық формаларының көріністерін, перинаталды және алыстағы нәтижелерді ұсынады. Дегенмен, ЦМВ инфекциясының асимптоматикалық нысандары үшін нақты диагностикалық критерийлер жоқ. ЦМВ инфекциясының әртүрлі формаларының этиопатогенетикалық терапиясының, болжамдық және алдын алу критерийлерінің нақты негіздемесі жоқ.

Жоғарыда аталған тапсырмалардың барлығы болашақтағы когорттық зерттеулерді қажет етеді.

Түйінді сөздер: *жаңа туған нәресте, туа біткен, перинаталдық, постнатальды цитомегаловирусты инфекция, симптоматикалық, симптомсыз түрі, жіктелуі*

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Финансирование: Авторы заявляют об отсутствии финансирования.
Конфликт интересов: Авторы заявляют об отсутствии конфликта интересов.
Прозрачность исследования: Авторы несут полную ответственность за содержание данной статьи.