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Congenital CMV infection- what we know about the symptoms, treatment and prevention? - Review of literature

Barbara Jaworska
Independent Health Care Center of the Ministry of Interior and Administration in Lublin
Grenadierów Street 3, 20-331 Lublin
https://orcid.org/0009-0000-9155-5084
barbaraewajaworska@gmail.com

Aldona Pażyra
Mazowiecki Szpital Wojewódzki im. św. Jana Pawła II w Siedlcach located at 26 Poniatowskiego Street, 08-110 Siedlce
https://orcid.org/0009-0001-6009-995X
aldona.pazyra16@gmail.com

Natalia Kusak
Samodzielny Publiczny Szpital Kliniczny Nr 4 w Lublinie located at 8 Doktora Kazimierza Jaczewskiego Street, 20-954 Lublin
https://orcid.org/0000-0001-5459-6768
natmarielea@gmail.com

Natalia Żak;
Mazowiecki Szpital Wojewódzki im. św. Jana Pawła II w Siedlcach located at 26 Poniatowskiego Street, 08-110 Siedlce
https://orcid.org/0009-0001-2454-8068
nzak93@gmail.com

Gabriela Różańska-Smuszkiewicz
Clinical Regional Hospital No. 2 named after St. Hedwig of Anjou in Rzeszów
Lwowska Street 60, 35-301 Rzeszów, Poland
https://orcid.org/0009-0005-3857-8830
gabrielarozanskaa@gmail.com

Paweł Smuszkiewicz-Różański
Health Care Centre in Strzyżów
700th Anniversary Street 1, 38-100 Strzyżów, Poland
https://orcid.org/0009-0009-3178-2029
pawels161@gmail.com

Weronika Kmiotek
Clinical Regional Hospital No. 2 named after St. Hedwig of Anjou in Rzeszów Lwowska Street 60, 35-301 Rzeszów
https://orcid.org/0009-0009-7699-0585
weronika55.12@o2.pl

Radosław Oronowicz
Regional Hospital named after Dr. H. Jankowski, 16 Szpitalna Street, 37-200 Przeworsk
https://orcid.org/0009-0008-8784-3858
Radoslaw.oronowicz@gmail.com

Dagmara Ragan
T. Marciniak Lower Silesian Specialist Hospital - Emergency Medicine Centre
General August Emil Fieldorf Street 2, 54-049 Wrocław
https://orcid.org/0009-0002-2423-0698
dagmara.ragan@gmail.com

Joanna Długosz
District Health Center - Specjalist Hospital in Brzeziny Maria Skłodowska-Curie Street 6, 95-060 Brzeziny, Poland
https://orcid.org/0009-0005-0922-6190
joanna.dlugosz123@gmail.com

Paweł Staszczak
SPZOZ University Clinical Hospital No. 1 named after Norbert Barlicki in Łódź.
dr. Stefana Kopcińskiego 22, 90-153 Łódź
https://orcid.org/0009-0005-8324-9956
pawel.staszczak@stud.umed.lodz.pl

Abstract
Introduction: Cytomegalovirus (CMV) is a double-strand DNA virus, member of the viral family known as *Herpesviridae* which is wide-spread. CMV infection is the most common congenital infection worldwide. Disease is mostly asymptomatic for healthy people, therefore is detected late, when the children start presenting symptoms. Unfortunately the congenital CMV infection leads to the serious health problems for infants. Detection of the virus is typically done through quantitative PCR assays. Infection especially affects nervous system and can present infant's deafness. Earlier it was equivalent with the children being deaf till the end of life, but nowadays thanks to the development of laryngological methods (ex. cochlear implantation) patients have chance to grow up correctly.
Material and methods: A literature search was conducted using Google Scholar, PubMed, and Web of Science databases. We searched articles by entering key words in the appropriate configuration: "CMV", "Congenital CMV infection", "valganciclovir", "infant's deafness". Scientific articles published between 1991–2023 were analyzed from all over the world and guidelines of Polish Society of Epidemiology and Infectious Diseases.
Conclusions: Currently we haven't got prevention towards congenital CMV, only the treatment for infants: valganciclovir. It stops development of severe symptoms. There are available analysis, where using valganciclovir during pregnancy reduces the possibility or soften the course of the congenital CMV infection , but it's not the obligatory guidelines. In many countries researchers want to conduct screening test for CMV IgG among the pregnant women.
Keywords: CMV, Congenital CMV infection, valganciclovir, infant's deafness

Introduction

Cytomegalovirus (CMV) is a wide-spread, double-stranded DNA virus, member of the viral family known as herpesviruses, *Herpesviridae*, or human herpesvirus-5 (HHV-5). It has manifestations ranging from asymptomatic to severe end-organ dysfunction in immunocompromised patients with congenital CMV (cCMV) disease. The virus is especially connected with the salivary glands. Approximately CMV infects up to 70% adults. Infection is mostly asymptomatic for healthy people, but congenital infection can be life-threatening or cause serious health problems like for example deafness, mucoepidermoid carcinoma or prostate cancer. It is also opportunistic pathogen in patients with a suppressed immune system, for example, from HIV, solid organ transplant, and bone marrow transplant. CMV often remains latent. Over 50% of the population has been exposed to CMV. Ways of transmission are: blood products (transfusions, organ transplantation), breastfeeding, viral shedding in close contact settings, perinatally, and sexual contacts. Most prevalent presentation of infection is CMV mononucleosis with symptoms like fever, rash and leukocytosis.

How can we detect the virus? If we suspect infection, we should prefer quantitative PCR assays. The results shows us if it is active or latent infection. Cidofovir, foscarnet, ganciclovir, valganciclovir are approved for the treatment.
In our article review we want to focus on congenital CMV infection, especially on how it affects newborn's life and ways of prevention or early treatment. We hope that our paper will be helpful for family doctors, pediatricians or gynecologists.

Clinical course

According to the research, about 40 % of women of reproductive age are seronegative to CMV. 1-3 % of them will develop CMV infection during pregnancy and 30-40% of maternal infections transmits to the fetus (1). The risk factors for acquiring CMV during pregnancy in seronegative women include increased exposures to CMV such as direct care of young children (teachers, pediatricians, nurses), sexually transmitted infections and other indices of sexual activity. (2) (3) Importantly, CMV reactivation or reinfection can occur in women who are seropositive prior to pregnancy. The risk of transplacental HCMV transmission is higher with primary infections, ranging from 21% in the first trimester to more than 50% in the third trimester, albeit with lower severity of cCMV(4). However, multiple reports have documented severe infections and long-term sequelae with second- and third-trimester infections.
Approximately 10−15% of infants with congenital CMV infection present symptoms like thrombocytopenia, petechiae, splenomegaly, hepatomegaly at birth. Also central nervous system is involved: microcephaly, intracranial calcifications, chorioretinitis, sensorineural hearing loss (5). Elevated levels of aspartate transaminase and conjugated hyperbilirubinemia, varied among different study populations and were evident in 23–80% of symptomatic newborns but are likely to return to normal within a few weeks.(6) Asymptomatic infants with CMV infection at birth have a better prognosis than symptomatic infants (risk for hearing loss: 7–15%).(7)

How to diagnose infection?

Screening test for CMV IgG for pregnant women is not obligatory within guidelines of Polish Society of Epidemiology and Infectious Diseases, but nowadays gynecologists recommend tests more often. Doctors should remember that even the patient has specific IgG prior to pregnancy or in early pregnancy, that the CMV infection in fetus is possible. (8)
The high risk group of patients are infants, whom mothers where diagnosed with CMV IgG during pregnancy. Diagnosis of congenital cytomegalovirus infection is possible during fetal life in children with ultrasound abnormalities. This method, as widely available, allows to the diagnose:

- cerebral ventriculomegaly,
- brain calcifications,
- microcephaly
- occipital horn anomalies
- noncerebral abnormalities such as echogenic bowel, intrauterine growth restriction (IUGR), hepatomegaly, ascites and cardiomegaly.(9)

Fetal growth restriction (FGR), ventriculomegaly, and abnormal placenta are the most common ultrasound findings associated with CMV infection. However, abnormalities are present in less than 50% of cases, meaning that a normal ultrasound does not rule out the possibility of congenital CMV infection. This underscores the limitation of relying solely on ultrasound for diagnosing CMV in fetuses. (10)
It is recommended to diagnose in CMV by amplification of viral DNA in urine, saliva or cerebrospinal fluid using PCR method.(11)(12)

Is prevention possible?
In 2005, researchers from Congenital Cytomegalovirus Collaborating Group, conducted a non-randomized study suggested that the administration of CMV-specific hyperimmune globulin (HIG) to pregnant women with primary CMV infection could lead to a significant decrease on the rate of mother-to-child-transmission (MTCT) (decreasing from 40 to 16%) and on the risk of congenital disease (decreasing from 50 to 3%)(13). However, in 2014 results of another trial from Japan showed that using HIG for the prevention of congenital CMV is not statistically significant (the group of pregnant women who had received HIG and the placebo group: 30% vs. 44%, P= 0.13)(14).
The findings of this systematic review and meta-analysis demonstrate that prenatal valganciclovir therapy following maternal CMV infection reduces the risk of congenital CMV infection and increases the likelihood of infection being asymptomatic. (15) Valganciclovir is a prodrug of ganciclovir, meaning it converts into the active form in the body. It also decrease the risk of severe adverse events in pregnant women. (7)(16)
Invention of the CMV vaccine is of the priorities for 21st century. (17)(18)
Prevention is important also for another reason: finances. Affected children require care and special therapeutic and educational services. According to statistics: in the United States the estimated cost of congenital CMV infection is up to $2 billion in 1992 dollars (which correlates with in excess of $3 billion today). (19)

Treatment
Currently we have five approved antiviral drugs for treating human cytomegalovirus (HCMV) infections, which fall into two categories:

1. Drugs inhibiting viral DNA synthesis: These include ganciclovir (GCV), valganciclovir (VGCV), cidofovir (CDV), and foscarnet (FOS). GCV and its prodrug VGCV are used to treat HCMV in immunocompromised patients and infants with congenital CMV (cCMV) infection. CDV treats HCMV retinitis in HIV patients, while FOS is effective against GCV-resistant HCMV infections.
2. Drugs inhibiting viral DNA packaging: Letermovir (LTV) is the only drug in this category, used to prevent HCMV infections in allogenic stem cell transplant recipients.

Among these, only GCV and VGCV are reported as safe and effective for treating symptomatic cCMV in infants. (20)
Treatment recommends gancyclovir (GCV) at a dose of 6 mg/kg, intravenously every 12 hours and/or valgancyclovir (VGCV) orally at a dose of 15 mg/kg/day every 12 hours for six weeks.

According to recommendations, children infected with CMV should be audiologicallly examined every 3-6 months until age 3, and then every 12 months until age 6, and an ophthalmologically examined once a year until age 5. All children with symptomatic CNS disease should have a neurodevelopmental evaluation every six months.(21)

Conclusion

Cytomegalovirus (CMV) is a significant public health concern, particularly for pregnant women and newborns. While the majority of infections are asymptomatic in healthy individuals, congenital CMV can lead to severe and lifelong complications. Early detection and prevention are crucial, yet challenging, given the variability in symptoms and the limitations of current screening practices. Although antiviral treatments like ganciclovir and valganciclovir offer some benefits, there remains an urgent need for more effective prevention strategies, including the development of a CMV vaccine. Ongoing research and increased awareness among healthcare providers are essential to improving outcomes for those affected by this pervasive virus.

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Methodology: N. Żak.
Software: P. Smuszkiewicz-Różański
Check: A. Pażyra, J. Długosz
Formal Analysis: B. Jaworska
Investigation: N. Kusak, A. Pażyra, N. Żak.
Resources: W. Kmiotek, N. Kusak, A. Pażyra, J. Długosz, N. Żak.
Writing–Rough Preparation: P. Staszczak, D. Ragan,
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Project Administrator: G. Różańska-Smuszkiewicz

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References

1. Yamamoto AY, Mussi-Pinhata MM, Boppana SB, Novak Z, Wagatsuma VM, Oliveira P de F, et al. Human cytomegalovirus reinfection is associated with intrauterine transmission in a highly cytomegalovirus-immune maternal population. Am J Obstet Gynecol. 2010;202(3):297.e1297.e8.
2. Fowler KB, Pass R. Sexually Transmitted Diseases in Mothers of Neonates with Congenital Cytomegalovirus Infection [Internet]. 1991. Available from: http://jid.oxfordjournals.org/
3. Plotkin SA, Boppana SB. Vaccination against the human cytomegalovirus. Vaccine. 2019 Nov 28;37(50):7437–42.
4. Pinninti S, Boppana S. Antiviral Treatment of Maternal and Congenital Cytomegalovirus (CMV) Infections. Vol. 15, Viruses. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
5. Lim Y, Lyall H. Congenital cytomegalovirus – who, when, what-with and why to treat? Journal of Infection. 2017 Jun 1;74:S89–94.
6. Suresh B. Boppana M, Robert F. Pass M, William J. Britt M, Sergio Stagno M, Charles A. Alford M. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J. 1992;12(2):93–9.
7. Daniel Williamson W, Percy AK, Yow MD, Gerson P, Catlin FI, Koppelman ML, et al. Asymptomatic Congenital Cytomegalovirus Infection Audiologic, Neuroradiologic, and Neurodevelopmental Abnormalities During the First Year From the Departments of Pediatrics
   (Drs Wil-liamson [Internet]. Available from: http://archpedi.jamanetwork.com/
8. Reccomendations on the diagnosis and treatment of CMV infections. Polish Society of Epidemiology and Infectious Diseases.
9. Naing ZW, Scott GM, Shand A, Hamilton ST, Van Zuylen WJ, Basha J, et al. Congenital cytomegalovirus infection in pregnancy: A review of prevalence, clinical features, diagnosis and prevention. Vol. 56, Australian and New Zealand Journal of Obstetrics and Gynaecology. Blackwell Publishing; 2016. p. 9–18.
10. Kim Y, Kim Y min, Kim DR, Kim HG, Sung JH, Choi SJ, et al. The Multifaceted Clinical Characteristics of Congenital Cytomegalovirus Infection: From Pregnancy to Long-Term Outcomes. J Korean Med Sci. 2023;38(32).
11. Rajewski P, Sobolewska--Pilarczyk M, Rajewski P. Congenital cytomegaly — recommendations for diagnosis and therapy. 2016; Available from: www.journals.viamedica.pl/forum_medycyny_rodzinnej
12. Shlonsky Y, Smair NS, Mubariki R, Bamberger E, Hemo M, Cohen S, et al. Pooled saliva CMV DNA detection: A viable laboratory technique for universal CMV screening of healthy newborns. Journal of Clinical Virology. 2021 May 1;138.
13. Nigro G, Adler SP, Torre R La, Best AM. Passive Immunization during Pregnancy for Congenital Cytomegalovirus Infection [Internet]. 2005. Available from: www.nejm.org

14. Yamada H, Morizane M, Tanimura K, Morioka I, Ebina Y, Matsuda H, et al. A trial of immunoglobulin fetal therapy for symptomatic congenital cytomegalovirus infection. J Reprod Immunol. 2012 Sep;95(1–2):73–9.
15. Pinninti S, Boppana S. Antiviral Treatment of Maternal and Congenital Cytomegalovirus (CMV) Infections. Vol. 15, Viruses. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
16. Nigro G, Muselli M. Prevention of Congenital Cytomegalovirus Infection: Review and Case Series of Valaciclovir versus Hyperimmune Globulin Therapy. Viruses. 2023 Jun 1;15(6).
17. Stratton KR, Durch JS, Lawrence RS. Vaccines for the 21st Century : a Tool for Decisionmaking. National Academies Press; 2000. 476 p.
18. Moseley P, Klenerman P, Kadambari S. Indirect effects of cytomegalovirus infection: Implications for vaccine development. Vol. 33, Reviews in Medical Virology. John Wiley and Sons Ltd; 2023.
19. Marsico C, Kimberlin DW. Congenital Cytomegalovirus infection: Advances and challenges in diagnosis, prevention and treatment. Vol. 43, Italian Journal of Pediatrics. BioMed Central Ltd.; 2017.
20. Tanimura K, Uchida A, Imafuku H, Tairaku S, Fujioka K, Morioka I, et al. The current challenges in developing biological and clinical predictors of congenital cytomegalovirus infection. Vol.
22, International Journal of Molecular Sciences. MDPI; 2021.
21. Shahar-Nissan K, Pardo J, Peled O, Krause I, Bilavsky E, Wiznitzer A, et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial [Internet]. Vol. 396, www.thelancet.com. 2020. Available from: www.thelancet.com