Cytomegalovirus Infection

Subjects: Pediatrics

Contributor: Bernhard Resch

Cytomegalovirus (CMV) is able to replicate in the breast milk of lactating mothers and thus the offspring might be affected by mild to severe symptoms of postnatal CMV disease in case of prematurity; not in term infants.

Keywords: cytomegalovirus ; infection ; preterm infants

1. Introduction

There is evidence of symptomatic cytomegalovirus (CMV) infection by viral replication during lactation of a CMV seropositive mother to the preterm neonate [1]. There is additional evidence that viral DNA has been detected from colostrum within the first days of life, and detection rates range between 20 and 58 percent [2][3]. Short-term morbidities associated with postnatal CMV infection include a wide range of symptoms, signs and diagnoses like sepsis-like syndrome (the most severe form), hepatopathia, hepatosplenomegaly, thrombozytopenia, neutropenia, hepatitis, myoclony, petechiae, respiratory distress syndrome, hyperbilirubinemia, bradycardia, apneas, cholestasis, distended belly, gray skin color, and elevated liver enzymes [4]. Long-term consequences of postnatal CMV infection still are in debate. For the term neonate, symptomatic CMV disease following postnatal infection has not been described, and is postulated as being a kind of natural immunization [5].

2. Postnatal Cytomegalovirus Infection

Cytomegalovirus (CMV) belongs to the Herpesviridae family and is classified as human herpesvirus type 5. CMV is a common virus for people of all ages provided the immune system is not compromised and prohibits illness. In healthy children and adults, symptoms of CMV infection are usually minimal, mimicking a mild upper respiratory tract infection (fever, sore throat, fatigue, swollen glands), and most of the patients are not aware that they are infected. Over half of adults have been infected with CMV by the age of 40 years; and the virus stays in the body for the whole life and can reactivate, for example during immunosuppressive therapy or in case of malignancies. Re-infection with a different strain of the virus is possible. Most people with CMV infection have no symptoms and aren’t aware that they have been infected. According to the Centers of Disease Control and Prevention, transmission routes include all body fluids, such as saliva, urine, blood, tears, semen, and breast milk [6]. CMV spreads from an infected individual by direct contact with saliva or urine (the most common sources are infants and young children), from breast milk to nursing infants, through sexual contact, and finally through transplanted organs and blood transfusions.

2.1. Short-Term Sequelae of Postnatal CMV Infection

Transmission route via breast milk is a kind of natural immunization of term infants, but this is not the case for the preterm infant. The sequelae of congenital CMV infection are well defined: They include microcephaly, seizure disorders, cognitive disability, developmental delay, and sensorineural hearing loss (SNHL) [7]. In contrast, sequelae of postnatal CMV infection via breast milk in the preterm infant is much less clear. Short-term morbidities including sepsis-like-syndrome and diverse end-organ disease manifestations are well recognized. However, the risks of adverse neurodevelopmental outcome are still the subject of debate and discussion. Interestingly, about 90 percent of preterm infants of seropositive mothers acquire CMV via lactation and breast feeding, but only a minority of infants develop signs and symptoms of CMV infection [4][7]. There exist many studies that endeavour to understand this phenomenon. Additionally, factors that modulate reactivation and cessation of viral shedding are the focus of research groups including cytokines, lactoferrin, and CD8+ T cells phenotypes [5]. Transmission of protective maternal antibodies starts at about the 29th week of gestation. This might be the reason why full term infants in general do not develop symptomatic disease [7]. Other manifestations of postnatal CMV have rarely been reported, including NEC [8].

In a study of infants below 1500 g birth weight, venous blood samples were tested for CMV IgG and IgM antibodies on the fifth and 30th day after birth from both mothers and infants (n = 38 and 42, respectively) [3]. Breast milk CMV DNA

detection by PCR and viral cultures were done until 12 weeks of age, as were urine samples of the infants for CMV culture. Thirty-six mothers (97.3%) were CMV-seropositive, and six infants became infected at a mean age of 77 days after birth. These infants more frequently had sepsis-like syndrome and direct hyperbilirubinemia, but neurodevelopmental outcomes at six months corrected for premature age did not differ between infected and non-infected infants [3].

More than 10 years ago, researchers published a review on transmission of human CMV via breast milk to the premature infant. Studies revealed CMV-positivity of the infants from CMV-IgG positive mothers from 5.7 to 58.6 percent; symptomatic CMV disease occurred in a median of 3.7 percent of the infants (range 0–34.5%), and severe sepsis-like syndrome in a median of 0.7% (range 0–13.8%) [4]. Few studies reported on long-term sequelae, and only weak evidence exists of mild neurologic and cognitive impairment without hearing impairment. Hamele et al. [9] reported on five preterm infants of 24 (+5) to 27 (+1) weeks of gestational age exhibiting severe morbidity and mortality associated with postnatal breast milk-acquired CMV infection. Since the early 1970s, eighteen infants had been identified when human breast milk first was known to be a potential source of CMV infection. In two cases out of these eighteen infants, the researchers provided no further details; five cases, with a gestational age of 29 to 33 weeks, did not experience severe disease (as defined as sepsis-like syndrome). The remaining 11 infants (four studies) had gestational ages ranging from 23 to 28 weeks (23, 25, 24 to 28, and 24.4 ± 0.5 weeks, respectively).

A Danish study included 26 preterm infants who received their mothers' own milk and looked at the frequency of CMV transmission, association with viral loads, and rates of sepsis-like symptoms [10]. Despite being a small study, nevertheless, four infants acquired CMV infection, with two of them exhibiting sepsis-like symptoms. The main finding was a higher viral load of mothers'own milk in infected compared to uninfected infants. Thus, viral loads and the amount of mothers'milk significantly increased the risk of CMV transmission to the preterm infant.

2.2. Potential Adverse Long-Term Neurodevelopmental of Postnatal CMV Infection

As already stated 10 years ago [4], there still exist very few studies addressing the long-term outcomes of preterm infants having had symptomatic postnatal CMV infection acquired via breast milk. From those studies available, the information is not conclusive. Thus, the principle question whether there remain neurodevelopmental sequelae or not is not answered simply by a "yes" or "no". Focusing on those studies dealing with breast milk-acquired CMV infection revealed five studies reporting long-term follow-up data of preterm infants with postnatal CMV infection [4]. The researcher found no association with sensorineural hearing loss and no differences regarding motor or speech development in comparison to reported controls. One small study, which found no differences in detailed examinations between postnatally infected and matched controls, reported that even having had severe sepsis-like syndrome, the risk was very low to detect neurologic or cognitive sequelae or to find an increased risk for hearing impairment [11].

Later studies, again from the Tübingen group of Hamprecht and colleagues, looked at more subtle deficits. Of 41 infants investigated at school age, all had normal hearing function and neurodevelopmental testing with the Kaufmann ABC test, and this did not differ between groups [11]. Further analysis of these patients revealed lower results in the simultaneous processing scales of the Kaufmann ABC tests [12]. Since these findings represent more complex cognitive function, they could be of some major concern for the individual. Another follow-up study of 42 infants found lower results in the simultaneous processing scales, even after considering socioeconomic status. Results for the sequential and achievement scales of the Kaufmann ABC were marginally reduced [13]. At adolescent age, a study with 42 former preterm infants compared the infants with term neonates using the Wechsler Intelligence Scale and the Developmental Test for Visual Perception. They scored significantly lower compared with the full-term neonates and had lower scores on overall cognitive abilities compared with the group of preterm infants without CMV infection [14].

Additionally, functional MRI examination showed differences in gray matter volume in several regions while performing different tasks. Hence, either activation differences were observed in the left hippocampus and the right anterior cingulate cortex during language tasks or within a small region of the occipital cortex during visuospatial tasks [15].

Looking at neonates who failed newborn hearing screening revealed a higher rate of 16% in the group with postnatal CMV infection compared with 9% in controls [16]. This study from the Pediatrix Medical Group network included more than 75,000 infants, with 273 infants having had postnatal CMV infection. The conclusion of this study is the fact that comprehensive audiological and neurodevelopmental follow-up data are needed in order to answer the questions regarding possible sequelae of postnatal CMV infection.

2.3. Are All Preterm Infants Prone to the Risk of Symptomatic CMV Disease?

As Alan Jobe [17] stated, severe cases of CMV pneumonia or sepsis-like syndrome can occur, but the small number of cases identified in this series is not enough to really estimate the general risk. It is still an unresolved problem as to whether the published evidence of the benefits of feeding preterm infants fresh CMV positive milk is worth the possible acquisition of symptomatic CMV disease by some of the infants. Until 2010 [18] researchers calculated only few cases of breast milk-acquired symptomatic CMV infection from the literature presenting as sepsis-like syndrome [3][9][19][20][21][22][23]. The gestational age (as shown above) was a maximum of 28 weeks. Therefore, it seems difficult to draw conclusions from such a small cohort of infants and generalize recommendations to all preterm infants. The majority of reported cases with severe postnatal CMV infection are the extremely low gestational age neonates.

References

1. Meier, J.; Lienicke, U.; Tschirch, E.; Krüger, D.H.; Wauer, R.R.; Prösch, S. Human cytomegalovirus reactivation during lactation and mother-to-child transmission in preterm infants. J. Clin. Microbiol. 2005, 43, 1318–1324.
2. Yasuda, A.; Kimura, H.; Hayakawa, M.; Ohshiro, M.; Kato, Y.; Matsuura, O.; Suzuki, C.; Morishima, T. Evaluation of cytomegalovirus infections transmitted via breast milk in preterm infants with a real-time polymerase chain reaction assay. Pediatrics 2003, 111, 1333–1336.
3. Jim, W.T.; Shu, C.H.; Chiu, N.C.; Kao, H.A.; Hung, H.Y.; Chang, J.H.; Peng, C.C.; Hsieh, W.S.; Liu, K.C.; Huang, F.Y. Transmission of cytomegalovirus from mothers to preterm infants by breast milk. Pediatr. Infect. Dis. J. 2004, 23, 848–851.
4. Kurath, S.; Halwachs-Baumann, G.; Müller, W.; Resch, B. Transmission of cytomegalovirus via breast milk to the prematurely born infant: A systematic review. Clin. Microbiol. Infect. 2010, 16, 1172–1178.
5. Fouda, G.G.; Martinez, D.R.; Swamy, G.K.; Permar, S.R. The impact of IgG transplacental transfer on early life immunity. Immunohorizons 2018, 2, 14–25.
6. Centers for Disease Control and Prevention. Cytomegalovirus (CMV) and Congenital CMV Infection. Available online: https://www.cdc.gov/cmv/clinical/overview.html (accessed on 4 March 2022).
7. Osterholm, E.A.; Schleiss, M.R. Impact of breast milk-acquired cytomegalovirus infection in premature infants: Pathogenesis, prevention, and clinical consequences? Rev. Med. Virol. 2020, 30, 1–11.
8. Patel, R.M.; Shenvi, N.; Knezevic, A.; Hinkes, M.; Bugg, G.W.; Stowell, S.R.; Roback, J.D.; Easley, K.A.; Josephson, C. Observational study of cytomegalovirus from breast milk and necrotising enterocolitis. Arch. Dis. Child. Fetal Neonatal Ed. 2019, 105, 259–265.
9. Hamele, M.; Flanagan, R.; Loomins, A.; Stevens, T.; Faircock, M.P. Severe morbidity and mortality with breast milk associated cytomegalovirus infection. Pediatr. Infect. Dis. J. 2010, 29, 84–86.
10. Volder, C.; Work, B.J.; Hoegh, S.V.; Eckhardt, M.C.; Zachariassen, G. Transmission of cytomegalovirus in fresh and freeze-thawed mother's own milk to very preterm infants: A cohort study. J. Perinatol. 2021, 41, 1873–1878.
11. Vollmer, B.; Seibold-Weiger, K.; Schmitz-Salue, C.; Hamprecht, K.; Goelz, R.; Krageloh-Mann, I.; Speer, C.P. Postnatally acquired cytomegalovirus infection via breast milk: Effects on hearing and development in preterm infants. Pediatr. Infect. Dis. J. 2004, 23, 322–327.
12. Bevot, A.; Hamprecht, K.; Krägeloh-Mann, I.; Brosch, S.; Goelz, R.; Vollmer, B. Long-term outcome in preterm children with human cytomegalovirus infection transmitted via breast milk. Acta Paediatr. 2012, 101, e167–e172.
13. Goelz, R.; Meisner, C.; Bevot, A.; Hamprecht, K.; Kraegeloh-Mann, I.; Poets, C.F. Long-term cognitive and neurological outcome of preterm infants with postnatally acquired CMV infection through breast milk. Arch. Dis. Child. Fetal Neonatal Ed. 2013, 98, F430–F433.
14. Brecht, K.F.; Goelz, R.; Bevot, A.; Krägeloh-Mann, I.; Wilke, M.; Lidzba, K. Postnatal human cytomegalovirus infection in preterm infants has long-term neuropsychological sequelae. J. Pediatr. 2015, 166, 834–839.
15. Dorn, M.; Lidzba, K.; Bevot, A.; Goelz, R.; Till-Karsten, H.; Marko, W. Long-term neurobiological consequences of early postnatal hCMV-infection in former preterms. Human Brain Mapp. 2014, 35, 2594–2606.
16. 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, 174, 133.
17. Jobe, A.H. CMV transmission in human milk. J. Pediatr. 2009, 154, A1.

18. Kurath, S.; Resch, B. Cytomegalovirus and transmission via breast milk: How to support breast milk to premature infants and prevent severe infection? Pediatr. Infect. Dis. J. 2010, 29, 680–681.
19. Miron, D.; Brosilow, S.; Felszer, K.; Reich, D.; Halle, D.; Wachtel, D.; Eidelman, A.I.; Schlesinger, Y. Incidence and clinical manifestations of breast milk-aquired cytomegalovirus infection in low birth weight infants. J. Perinatol. 2005, 25, 299–303.
20. Doctor, S.; Friedman, S.; Dunn, M.S.; Asztalos, E.V.; Wylie, L.; Mazzulli, T.; Vearncombe, M.; O'brien, K. Cytomegalovirus transmission to extremely low-birthweight infants through breast milk. Acta Paediatr. 2005, 94, 53–58.
21. Vochem, M.; Hamprecht, K.; Jahn, G.; Speer, C.P. Transmission of cytomegalovirus to preterm infants through breast milk. Pediatr Infect. Dis. J. 1998, 17, 53–58.
22. Hamprecht, K.; Maschmann, J.; Vochem, M.; Dietz, K.; Speer, C.P.; Jahn, G. Epidemiology of transmission of cytomegalovirus from mother to preterm infant by breastfeeding. Lancet 2001, 357, 513–518.
23. Rieger-Fackeldey, E.; Genzel-Boroviczény, O.; Schulze, A. Schwere systemische Zytomegalie-Virusinfektion Frühgeborener über die Muttermilch. Mon. Kinderheilkd 2001, 149, 1059–1062.
