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Current Opinion of Congenital CMV Transmissions, Clinical Manifestation Treatment, and Prevention

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Abstract

Congenital cytomegalovirus (CMV) infection is the most common congenital infection with a high burden of disease globally. Epidemiologically the seroprevalence of CMV infection in adults are varied between country and country. However, the seroprevalence of CMV in adults and the incidence of congenital CMV infection are highest in developing countries. Congenital CMV infection is one of the causes of hearing, cognitive, and motor impairments in newborns. The standard laboratory test for diagnosing and confirmatory test of congenital CMV infection is polymerase chain reaction (PCR) from the sample collected from saliva 3 hours after breastfeeding and urine sample. It is recommended to treat all infants with moderately to severely symptomatic at a time of delivery and infants with hearing loss. The dose for oral valganciclovir treatment is recommended to be 16 milligrams per kilogram twice a day for six months and 12 milligram per kilogram twice a day for intravenous ganciclovir. Intravenous ganciclovir should be reserved for the infant who are not able to take oral treatment. Apart from pharmacological intervention, the health education of pregnant mothers may play a key role in combating the burden of disease, especially in developing countries.

Keywords: Congenital cytomegalovirus; Cytomegalovirus; Primary maternal cytomegalovirus infection; Congenital infection; Transplacental transmission; Hearing loss; Vision loss

INTRODUCTION

Cytomegalovirus (CMV) is a double-stranded DNA virus and is the largest of the Herpesviridae family [1]. CMV infection occurs in people of all ages globally. The virus is reported to be infecting almost fifty percent of the community in high-income countries in their adulthood and around everybody in their early childhood in low- and middle-income countries[2,3]. Recent studies have indicated that CMV seroprevalence is certainly associated with poverty and poor income societies[4]. CMV transmitted through direct contact with body fluids, such as blood, urine, semen, saliva, vaginal fluids, and breast milk. Another possible transmission may occur through breastfeeding, blood transfusions, organ transplants, and maternal infection[5]. Once one gets a primary infection, the viruses can spread to varieties of human body systems and remain inert for life in which referred to as a latent infection. However, the latent infection can be reactivated later in life and disease may develop again.

Primary infection with CMV is not uncommon and may be asymptomatic however is one of the common causes of a flu-like syndrome (mononucleosis) an illness similar to Epstein-Barr virus, but results of a heterophile antibody test for EBV will be negative[5,6]. The virus makes the biggest impact when it encounters immature or compromised immune systems, as in developing fetuses or immunocompromised persons[6]. Congenital cytomegalovirus is an infection that can appear when a newborn is infected with a virus known as cytomegalovirus prior to childbirth. However, the mother may not have symptoms and not aware that she is carrying the CMV. Nevertheless, most infected babies with CMV during birth do not develop symptoms. Congenital CMV condition accounts for thousands of babies being born with a disability or developing permanent disability like hearing loss, vision loss, cerebral palsy and cognitive impairment globally each year[7-9]. A baby may acquire a virus following primary infection of the pregnant mother who becomes seroconverted or following recurrence infection of the pregnant mother of reinfection during pregnancy[10-11].

The aim of this article is to review and summarize worldwide studies report published on congenital CMV. Our special attention was epidemiology, diagnosis, treatment outcome, complication and prevention of mother to child transmission.

Epidemiology and burden of disease

Congenital cytomegalovirus (CMV) infection is the most common congenital infection globally, but its prevalence is being reported to range from 0.2% to 2% with the average 0.65% However, most of these estimates reported in the publication from developed countries nevertheless, prevalence of congenital CMV in African countries population somehow varies due to data sparsity of data presented in different publications Table 1 The CMV infection prevalence at a time of birth based entirely on the diagnostic criteria and diagnostic tools used to detect the evidence of the presence of infections. There are varieties of diagnostic criteria that defined the presence of CMV infection based on the culture test from the sample taken from urine, and saliva as well as a positive result from Polymerase chain reaction (PCR). Given the fact that there is possibility of postnatal cytomegalovirus (CMV) infection from seropositive mothers through breastfeeding, consequently the recommended time for diagnosis of congenital CMV should be within 3 weeks from the time of birth [14-17].

No:	Author	Year	Country	Study population	Prevalence
1	Manicklal et al[2]	2014	South Africa	748	2.9
2	Mwaanza et al.[49]	2014	Zambia	395	3.8
3	Schopfer et al.[50]	1978	Ivory Coast	2,032	1.4
4	van der Sande et al.[51]	2007	Gambia	741	5.4
5	Yamamoto et al.[52]	2011	Brazil	12,195	1.0
6	Zhang et al.[53]	2007	China	1,159	6.1
7	Tsai et al.[54]	1996	Taiwan	1,000	1.8
8	Dar et al.[55]	2008	India	423	2.1
9	Ahlfors et al.[14]	2008	Sweden	16,474	0.5
10	Gaytant et al.[15]	2005	The Netherland	7,793	0.9
11	Granström et al.[17]	1977	Finland	148	2
12	MacDonald et al.[56]	1978	England Manchester	6,051	0.4
13	Griffiths et al.[57]	1991	England London	2,737	0.3
14	Andersen et al.[58]	1979	Denmark	3,060	0.4
15	Natali et al.[59]	1997	Italy Parma	1,045	0.57
16	Montgomery et al.[60]	1980	USA-Texas	461	0.6
17	Stagno et al.[18]	1986	USA-Alabama	2,579	1.4
18	Murph et al.[61]	1997	USA-Iowa	7,229	0.48
19	Larke et al.[62]	1980	Canada	15,212	0.42
20	Luchsinger et al.[63]	1996	Chile	218	1.8
21	Kamada et al.[64]	1983	Japan	2070	0.5
22	Sohn et al.[65]	1992	Korea	514	1.2
23	Hatherley et al.[66]	1985	Australia	47,320	0.03
24	Noyola et al.[45]	2003	Mexico	560	0.9
25	Estripeaut et al.[67]	2007	Panama	317	0.6

Table 1: Congenital CMV prevalence worldwide as reported by publication.

Mother to child transmission

Mother to child CMV infection transmission can be divided into three categories, before birth (transplacental), during birth (intrapartum) after birth (postpartum). The overall mother to child transmission of CMV among pregnant women with the maternal primary infection is reported to be around 35%[18]. However, the transplacental transmission rate is reported to be increased as the gestation age increases. The rate at first trimester is reported to be around 20% which lower compared to the third-trimester rate which is reported to be approximately 75%[19,20]. The infection during the first trimester especially with the maternal primary infection is considered to be more related to the disability in which a newborn may likely develop central nervous system disability, impaired vision or hearing loss[21,22]. Apart from primary infection transmission, there is a possibility of recurrent infection within which a previously infected mother with strong immunity may pass the infection during pregnancy development and this type of transmission is reported to be approximately 0.1% up to 1% with the average of 0.6%. Apart from the transplacental transmission, during birth (intrapartum) transmission also may take place as a result of the existence of the virus in the birth canal. The virus has been reported to be a presence in the birth canal especially in women with CMV seropositive as results of cervicovaginal viral shedding. Some report from publication indicates that viral shedding is more common in women with HIV infection especially for those with low CD4 count[23,24]. The commonest mode of transmission after birth (postpartum) is breastfeeding. It is reported that CMV DNA can be detected in 95% of milk from breastfeeding mothers who tested CMV seropositive[25,26] The infant can acquire infection through reactivation of previously infected breastfeeding

mothers after primary infection. In general, breastfeeding has a major contribution when it comes to postnatal CMV infection. In the first 3 months of postpartum the prevalence of CMV infection is reported to be 27% among infants born in seropositive mothers[27]. The study conducted by Drworsky et al[28]. reported that 32% of seropositive mothers pass the virus in breast milk in which 69% of their infants later were found to infected. Nevertheless, the maternal immunity shows no impact in preventing the virus from passing in milk as well as it doesn't prevent transmission of infection to the newborn. However, the child may not develop any kind of illness her/his immune system become or is deficient.

Clinical presentation

Clinical presentation of congenital CMV can be categories into asymptomatic, asymptomatic with isolated sensor neural hearing, mild symptomatic and moderately to severely symptomatic congenital CMV based on the recommendation from world-renowned CMV expertise in 2017 following the congenital CMV international conference that took place in 2015 [29] (Table. 2)

No.	Categories	Definition
1	Asymptomatic	Baby who have no obvious defect at birth and have usual hearing
2	Asymptomatic with isolated sensor neural hearing	Babies who apart from hearing apparently clinical symptoms
3	Mild symptomatic	Baby who presented with one or two isolated mild or transient manifestations.
4	Moderately to severely symptomatic	Babies with CMV and presented with multiple manifestations or have central nervous system (CNS) involvement.

Based on the above categorical table and corresponding definitions, the clinical presentation of congenital CMV shows a wide range of variation in its manifestation. However approximately 85% to 90% of the infected baby are asymptomatic at birth and the remaining 10% to 15% are presenting with signs at birth which include rash, jaundice, microcephaly, intrauterine growth restriction which resulting to low weight babies, hepato-splenomegaly, seizures and inflammation of the retina (retinitis). Among those symptomatic babies, approximately 50% will have a developmental defects such as hearing loss, developmental and motor delay and vision loss, which have been associated with infection earlier in the pregnancy. In severe cases of intrauterine infection, CMV can cause miscarriage (pregnancy loss).

Diagnosis

The standard laboratory test for diagnosing and confirmatory tests of congenital CMV infection is polymerase chain reaction (PCR). The sample collected from saliva used as a diagnostic test and sample from urine usually collected and tested for confirmation. However, urine is not superior to saliva, consequently is recommended to do both to avoid false-positive results from the saliva sample because most of CMV seropositive mothers are shading CMV virus through there breast milk and if a sample was taken shortly after breastfeeding the results may show positive but the virus may come from the mother's milk and not baby saliva. To avoid a false positive from the saliva sample, it is recommended the specimen be taken more than one hour after breastfeeding. The test for diagnosis of congenital CMV should be within 3 weeks from the time of birth[30,31]. Any diagnosis that will be performed after 3 weeks also may give contradicting results based on whether it is congenital or post-partum infection transmission.Generally, PCR laboratory test results is superior to viral culture test for diagnosis of congenital CMV, but any positive results from PCR test should be verified by repeating the sample [32,33] Currently it has been proved from the study reported by Liesnard et al, that sample obtained from amniotic fluid can be used as a prenatal diagnostic sample to show the presence of intrauterine transmission. In their study which followed 237 pregnant mothers who have been suspected to have CMV or confirmed to have primary CMV. In their results, they showed that from the amniotic sample the PCR sensitivity was 80% and 100% specificity. According to their findings, the best gestation age for performing the test was recommended to be 21 weeks. However, in early pregnancy, the test sensitivity may become less sensitive.

Complications

Hearing Loss

One of the long term sequelae of congenital CMV is hearing loss. Hearing loss may progress from mild to severe in early childhood especially the first two years of baby growth and development[34]. During this period is when the child learning language, therefore, this is a critical period in overall development because hearing loss can affect a child's ability to develop speech, language, and social skills. However, the hearing loss manifestation median age is 33 months and 44 months for symptomatic and asymptomatic respectively, therefore for every baby with CMV infection should receive consecutive audiological monitoring. In their publication, Fowler et al recommended that for CMV infected babies require a full audiological evaluation from birth to six weeks after birth. The recommended set of the test includes evaluation tests and follow-up tests. In evaluation test, the baby should receive the auditory brainstem response (ABR) a test that tells how the inner ear, called the cochlea, and the brain pathways for hearing are working, the OAE (Otoacoustic Emissions) test to checks part of the inner ear's response to sound., tympanometry, and acoustic reflexes. Further follow-up is performed through visual reinforcement audiometry (VRA) or conditioned play audiometry[35]. Congenital CMV is considered a leading cause of nongenetic related hearing loss in developed countries while it is the leading cause in developing countries[36]. Since CMV-related hearing loss may progress from mild to severe in early childhood especially the first two years of baby growth, special attention should be given to children with hearing aids to ensure proper amplification if their hearing levels fluctuate.

Vision loss

Vision loss is reported to be less common in occurrence compared to hearing loss or cognitive deficit but it is a significant disability that can be caused by congenital CMV infection. However, vision loss tends to be much less encounter in children with asymptomatic congenital CMV compared to those with symptomatic at birth[37]. However, some published studies have been reporting the vision loss secondary to congenital CMV in children who were asymptomatic at birth [38-41]. Vision loss just like hearing loss may manifest at a time of birth or it may manifest later in life[42]. A study conducted by Jin et al [43]. reported that severe form of visual impairment secondary to congenital CMV infection is caused by cortical visual impairment, optic nerve atrophy, uveitis, strabismus, and nystagmus. However, the visual impairment associated with congenital CMV infection is reported to be stable or improve in infancy. Nevertheless, it is recommended annually ophthalmologic follow-up through examination particularly for those infants with symptomatic congenital CMV infection who were detected with visual disorders.

Developmental and Motor Delay

Neurodevelopmental long-term sequelae are a major concern with congenital CMV, particularly when the infant is symptomatic at birth. Central nervous system manifestation in congenital CMV infection depends on the gestation age maternal-fetal transmission occurrence. However intrauterine transmission that occurs in early gestation age most likely will cause ventriculomegaly, lissencephaly, delayed myelination, cerebellar hypoplasia, and calcifications, while the late transmission may associate with periventricular cysts, polymicrogyria, cerebellar hypoplasia, white matter abnormalities, less severe ventriculomegaly, and dysmyelination. Pinninti et al in there study reported that CNS manifestation of congenital CMV in symptomatic patients were seizures, lethargy or hypotonia, microcephaly, poor suck, and neuro-radiological findings. Nevertheless, these babies have a high chance of developing a long-term neurological developmental defects [45].

Treatment

The treatment and prevention of CMV virus infection are through antiviral drugs such as ganciclovir and valganciclovir. However, valganciclovir is a biologically inactive form of ganciclovir which can be metabolized in the intestine and liver to become ganciclovir. Evidence from many publications has demonstrated that intravenous ganciclovir treatment for six weeks resulted in improvement of hearing outcome [46]. However, the treatment was found to cause neutropenia, anemia, and thrombocytopenia after a course of treatment. A comparison study of valganciclovir compared to ganciclovir was able to demonstrate the same outcome with valganciclovir oral treatment which has much less adverse reaction. Nevertheless, intravenous ganciclovir treatment has been reported to show significant improved neurodevelopmental outcomes. Currently, CMV infection treatment regimen recommended treating all infants with moderately to severely symptomatic at a time of delivery, and infants with hearing loss. The dose for oral valganciclovir treatment is recommended to be 16 milligrams per kilogram twice a day for six months and 12 milligram per kilogram twice a day for intravenous ganciclovir. Intravenous ganciclovir should be reserved for an infant who is not able to take oral treatment.

Preventions

CMV virus is commonly found in high amounts particularly in saliva, urine or other body fluid. Avoiding contact with saliva and urine from young children might reduce the risk of CMV infection. Healthcare providers should follow standard precautions. Vaccines are still in the research and development stage. The key interventional that might result in a big impact on reduction of congenital MCV disease can be divided into the prevention of primary infection of the mother, prevention of mother to child transmission, neonatal screening, and early detection and treatment.

Prenatal serological screening might contribute highly to identifying infected population but still, there is no clear intervention that is proven efficacy for pregnant women with primary infection. However, it has been proven that the CMV-specific hyperimmune globulin (HIG) administered to pregnant mothers with primary CMV infection resulted in significant reduction of mother to the child transmission rate. The results showed both decreases in transmission from 40% to 16% and decrease on the risk of congenital disease from 50% to 3%) [47] Nevertheless, a study by Leruez et al[48]. show efficacy of high dose administration of valacyclovir among pregnant mothers with a moderately CMV infected fetus. Vaccine for CMV virus still at its infancy level and the results are waited to be seen.

The CMV virus complex nature of protective immunity with distinct viral strains is a big challenge for the development of an effective vaccine against CMV infection. However, a phase II study of a gB/MF59 vaccine in post-delivery women showed efficacy around 50% against primary infection, with the protection observed predominantly in the first 12 months after vaccination. The best cost-effective interventions for the prevention of both primary maternal CMV infection and congenital CMV infection is the health education of pregnant mothers. Pregnant mothers should receive proper health education regarding sources of infection related to exposure and behavioral changes that may prevent CMV viral contact. Basic personal hygiene like hand washing before contacting and after contacting children especially after contacting children urine during diapers changing. Many mothers have a tendency of kissing their babies, this should be avoided as well as baby food utensils should be kept separately.

CONCLUSION AND RECOMMENDATION

Congenital cytomegalovirus (CMV) infection is the most common congenital infection with a high burden of disease globally. Congenital CMV infections are the result of intrauterine transmission-based either primary or recurrent infection. Epidemiologically the seroprevalence of CMV infection in adults are varied between country and country. However, the seroprevalence of CMV in adults and the incidence of congenital CMV infection are highest in developing countries. Congenital CMV infection is one of the causes of hearing, cognitive, and motor impairments in newborns. The standard laboratory test for diagnosing and confirmatory test of congenital CMV infection is polymerase chain reaction (PCR) whereby samples collected from saliva 3 hours after breastfeeding and sample from urine usually collected and tested. It is important for the clinician to treat all infants with moderately to severely symptomatic at a time of delivery and infants with hearing loss. The dose for oral valganciclovir treatment is recommended to be 16 milligrams per kilogram twice a day for six months and 12milligram per kilogram twice a day for intravenous ganciclovir. Intravenous ganciclovir should be reserved for an infant

who is not able to take oral treatment. While immunization is still undergoing development, but health education of pregnant mothers may play a key role in combating the burden of disease especially in developing countries. Basic personal hygiene like hand washing before contacting and after contacting children has been proven to be a cost-effective intervention.

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