J Korean Med Sci. 2023 Aug 14;38(32):e249
https://doi.org/10.3346/jkms.2023.38.e249
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Obstetrics & Gynecology

The Multifaceted Clinical Characteristics of Congenital Cytomegalovirus Infection: From Pregnancy to Long-Term Outcomes

Yejin Kim,[1] **Yoo-min Kim**,[2] **Doo Ri Kim**,[3] **Han Gyeol Kim**,[4] **Ji-Hee Sung**,[1] **Suk-Joo Choi**,[1] **Soo-young Oh**,[1] **Yae-Jean Kim**,[3] **Yun Sil Chang**,[3] **Dongsub Kim**,[4] **Jung-Sun Kim**,[5] **Il Joon Moon**,[6] **and Cheong-Rae Roh** [1]

[1]Department of Obstetrics and Gynecology, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea
[2]Department of Obstetrics and Gynecology, Chung-Ang University College of Medicine, Seoul, Korea
[3]Department of Pediatrics, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea
[4]Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, Korea
[5]Department of Pathology, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea
[6]Department of Otorhinolaryngology-Head and Neck Surgery, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea

Received: Nov 24, 2022
Accepted: May 17, 2023
Published online: Jul 25, 2023

Address for Correspondence:
Soo-young Oh, MD, PhD
Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: ohsymd@skku.edu

Yae-Jean Kim, MD, PhD
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: yaejeankim@skku.edu

ORCID iDs
Yejin Kim
https://orcid.org/0000-0002-9425-2609
Yoo-min Kim
https://orcid.org/0000-0001-9797-006X
Doo Ri Kim
https://orcid.org/0000-0001-5233-4043
Han Gyeol Kim
https://orcid.org/0000-0001-9228-2364

ABSTRACT

Background: The aim of this study was to capture multifaceted clinical characteristics of congenital cytomegalovirus (CMV) infection from diagnosis to treatment using a multidisciplinary approach including obstetrics, pediatrics, pathology, and otorhinolaryngology-head and neck surgery.

Methods: This is a retrospective study including 30 consecutive cases of congenital CMV infection that were diagnosed at a single tertiary hospital located in Seoul, Korea from January 2009 to December 2020. Congenital CMV infection was defined as a positive result by polymerase chain reaction from urine, saliva or cerebrospinal fluid or positive CMV IgM from neonatal blood sampled within 3 weeks after birth. All cases were analyzed with respect to whole clinical characteristics from diagnosis to treatment of congenital CMV by a multidisciplinary approach including prenatal sonographic findings, maternal immune status regarding CMV infection, detailed placental pathology, neonatal clinical manifestation, auditory brainstem response test, and antiviral treatment (ganciclovir or valganciclovir). Long-term outcomes including developmental delay and hearing loss were also investigated.

Results: The total number of births during the study period in our institution was 19,385, with the prevalence of congenital infection estimated to be 0.15%. Among 30 cases of congenital CMV, the median gestational age at delivery was 32.2 weeks [range, 22.6–40.0] and 66.7% of these infants were delivered preterm at less than 37 weeks. Suspected fetal growth restriction was the most common prenatal ultrasound finding (50%) followed by ventriculomegaly (17.9%) and abnormal placenta (17.9%), defined as thick placenta with calcification. No abnormal findings on ultrasound examination were observed in one-third of births. Maternal CMV serology tests were conducted in only 8 cases, and one case each of positive and equivocal IgM were found. The most common placental pathologic findings were chronic villitis (66.7%) and calcification (63.0%), whereas viral inclusions were identified in only 22.2%. The most common neonatal manifestations were jaundice (58.6%) followed by elevation of aspartate

Ji-Hee Sung
https://orcid.org/0000-0002-9658-2898
Suk-Joo Choi
https://orcid.org/0000-0002-8946-4789
Soo-young Oh
https://orcid.org/0000-0003-3002-0048
Yae-Jean Kim
https://orcid.org/0000-0002-8367-3424
Yun Sil Chang
https://orcid.org/0000-0001-9201-2938
Dongsub Kim
https://orcid.org/0000-0002-9836-6769
Jung-Sun Kim
https://orcid.org/0000-0002-7221-2737
Il Joon Moon
https://orcid.org/0000-0002-3613-0734
Cheong-Rae Roh
https://orcid.org/0000-0002-5266-6168

Funding

This work was supported by the research grant from the Creative Research Program funded by Samsung Medical Center, the Korea Health Technology R&D Project through the Korea Health Industry Development Institute funded by the Ministry of Health & Welfare, Republic of Korea [grant no: HI20C0377] and the National Research Foundation of Korea grant funded by the Korea government Ministry of Science and ICT [grant no: NRF-2019R1A2C1009547].

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Oh SY. Data curation: Kim Y, Kim YM, Kim DR, Kim HG, Kim JS. Formal analysis: Kim Y. Methodology: Kim YJ, Oh SY. Investigation: Kim Y, Kim YM, Kim DR, Kim HG, Kim JS. Writing - original draft: Kim Y. Writing - review & editing: Sung JH, Choi SJ, Oh SY, Kim YJ, Chang YS, Kim DS, Kim JS, Moon IJ, Roh CR.

aminotransferase (55.2%) and thrombocytopenia (51.7%). After excluding cases for which long-term outcomes were unavailable due to death (n = 4) or subsequent follow up loss (n = 3), developmental delay was confirmed in 43.5% of infants (10/23), and hearing loss was confirmed in 42.9% (9/21) during the follow-up period. In our cohort, 56.7% (17/30) of neonates were treated for congenital CMV with ganciclovir or valganciclovir.

Conclusion: Our data show that prenatal findings including maternal serologic tests and ultrasound have limited ability to detect congenital CMV in Korea. Given that CMV is associated with high rates of developmental delay and hearing loss in infants, there is an urgent need to develop specific strategies for the definite diagnosis of congenital CMV infection during the perinatal period by a multidisciplinary approach to decrease the risks of neurologic impairment and hearing loss through early antiviral treatment.

Keywords: Cytomegalovirus; Congenital Infection; Infection Ultrasound; Ganciclovir; Valganciclovir; Developmental Delay; Hearing Loss

INTRODUCTION

Congenital cytomegalovirus (CMV) infection affects 0.7% of live births worldwide, and varies from 0.2 to 2.0% of live births according to region.[1,2] About 10% of live births with congenital CMV have variable clinical manifestations during the newborn period. According to a recent multicenter research conducted in Korea, the birth prevalence of symptomatic congenital CMV infection was 0.11% from 2009 to 2015.[3] However, the majority of congenital CMV-infected newborns are asymptomatic. Approximately 50% of symptomatic infants will have permanent neurologic sequelae, and 10% of infants asymptomatic in the neonatal period develop hearing loss later due to CMV infection.[4-6] The most common neurologic sequelae among neonates with congenital CMV infection is hearing loss followed by cognitive impairment, retinitis, and cerebral palsy.[4]

Congenital CMV infection occurs due to vertical transmission through the placenta during pregnancy. In primary maternal CMV infection, the vertical transmission rate of CMV reaches 30% to 40%, compared with only 1% following secondary maternal CMV infection.[7] Moreover, severe symptoms at birth and long-term sequelae are seen more frequently among children who born to women with primary infection during pregnancy.[8] However, the risk of actually acquiring congenital CMV during pregnancy is relatively high for seropositive women, in nation-wide sight.[8] In Korea, since seropositivity for CMV IgG is as high as 95.8% among women of childbearing age,[9,10] it can be assumed that secondary infection will be more significant and diagnosis by maternal serologic tests has limited value.

Unfortunately, there have been very few reports examining congenital CMV in Korea and there are no national data assessing the prevalence of congenital CMV infection during pregnancy. Recently, otolaryngological analyses found that 33.3% of individuals with congenital CMV infections had sensorineural hearing loss (SNHL), confirming CMV as a significant cause of neonatal and infant SNHL in Koreans as well.[11] Meanwhile, recent pediatric research identified a correlation between brain magnetic resonance imaging and neonatal neurologic outcomes (or SNHL).[12] However, these studies did not include clinical information regarding maternal immune status or neonatal manifestations. The whole spectrum of congenital CMV infection from pregnancy to long-term outcomes of children remains poorly understood.

The aim of this study was to analyze multifaceted clinical characteristics of congenital CMV infection from diagnosis to treatment by a multidisciplinary approach including obstetrics and gynecology, pediatrics, pathology, and otorhinolaryngology-head and neck surgery.

METHODS

This is a retrospective descriptive study including 30 consecutive cases of congenital CMV infection diagnosed in our institution, a tertiary hospital located in Seoul, Korea from January 2009 to December 2020.

Congenital CMV infection was defined as a positive result by polymerase chain reaction (PCR) or CMV IgM serology test from neonatal blood, urine, saliva or cerebrospinal fluid within 3 weeks after birth. During the study period, diagnostic tests were performed within 3 weeks after birth for neonates who satisfy one or more of followings: maternal symptoms or sign which suggest primary CMV infection, one or more prenatal abnormal sonographic findings (suspected fetal growth restriction [FGR], abnormal placenta, ventriculomegaly, ascites, pericardial effusion, echogenic bowel, and hydrops) or one or more postnatal characteristics which suggest congenital CMV infection (small for gestational age [SGA], microcephaly, intracranial calcification, ventriculomegaly, jaundice, aspartate aminotransferase [AST] elevation, thrombocytopenia, retinitis, and seizure). After patient selection, we retrospectively reviewed medical records and extracted data for whole clinical characteristics from suspicion during pregnancy to treatment after birth of congenital CMV infection as obstetrics and gynecology and pediatrics aspects. We also obtained data of infant on multidisciplinary approach including pathology, and otorhinolaryngology-head and neck surgery, where possible. Maternal characteristics and obstetrical outcomes included parity, preeclampsia, gestational diabetes, delivery mode, and results of maternal CMV serology tests (when available). Prenatal sonographic findings suggesting congenital CMV infection included suspected FGR, abnormal placenta, ventriculomegaly, ascites, pericardial effusion, echogenic bowel, and hydrops. FGR was defined as fetal ultrasound estimated birth weight < 10th percentiles for gestational age. Abnormal placenta was defined as placentomegaly or placental calcification (≥ grade 2). Placentomegaly was diagnosed if the placental thickness exceeded 4 cm in the second trimester or 6 cm in the third trimester. Placental calcification was classified by the Grannum grading system as previously defined.[13] In detail, grade 2 displays echogenic lines throughout all depths and hyperechoic, comma-shaped curves extending from the chorionic plate into the placenta and grade 3 shows extensive basal echogenicity and complete indentations of the chorionic plate. Clinical characteristics of infants included sex, birth weight, SGA, microcephaly, intracranial calcification, ventriculomegaly, jaundice, AST elevation,[14] thrombocytopenia, retinitis, seizure, and death. SGA was defined as neonatal birth weight < 10th percentiles for gestational age, and described according to a reference table with data from the Korean Statistical Information Service (2008–2012).[15] Microcephaly was defined when a pediatric examination within one year of age confirmed that the head circumference was less than 3 standard deviations for the corrected age at least once. Intracranial calcification and ventriculomegaly were evaluated by first brain sonographic examination within a month of age. Jaundice was defined when phototherapy was administered. AST elevation was defined as AST > 40 U/L within a month of age. Thrombocytopenia was defined as platelet count less than 100,000/mm^3. The presence of seizure was judged according to the presence of symptoms or EEG abnormalities. To confirm CMV retinitis, ophthalmic examinations were

https://doi.org/10.3346/jkms.2023.38.e249

performed during hospitalization or through outpatient clinics, and the diagnosis was made by an ophthalmologist.

Placental findings were assessed by a single pathologist (JSK) who specialized in placental pathology. The histology of the placenta was reviewed after study enrollment to evaluate chronic villitis, plasma cells, viral inclusions, chorionic vasculitis, calcification, hemosiderin, stromal fibrosis, delayed maturation, acute chorioamnionitis, and funisitis, which are reported to be common histologic findings of CMV infected placenta.[16]

As for long-term outcomes, developmental delay and hearing loss were also investigated. Developmental delays were clinically assessed by pediatricians or rehabilitation physicians in children at least 1 year of age and/or by Denver II or Bayley II/III tests within 3 years of age. Hearing loss was evaluated as a long-term outcome only when the results of otolaryngology examinations after at least 1 year of age were known. In Korea, the automated otoacoustic emissions (OAE) or automated auditory brainstem response (AABR) test is implemented as a newborn hearing screening test after birth.

After a diagnosis of congenital CMV infection, postnatal antiviral therapy was started according to the decision of pediatric infection specialist. There was a change in the treatment regimen during the follow-up period. Until March 2015, patients were treated with intravenous ganciclovir for 6 weeks. However, six months of oral valganciclovir treatment was reported to improve long-term outcomes of symptomatic congenital CMV disease in 2015.[17] From November 2015 on, we applied treatment with oral valganciclovir for six months for moderate to severely symptomatic congenital CMV disease.

Categorical statistics were expressed as number (percentage). Continuous data were expressed as median and range. The presence of abnormal histological findings of the placenta according to long-term neurologic impairment was assessed using Chi-square or Fisher's exact tests. A two-tailed *P* value below 0.05 was considered statistically significant. All statistical analyses were carried out using the Statistical Package for Social Sciences version 25 (SPSS Statistics; IBM, Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center and the requirement for informed consent was waived (IRB No. 2019-01-009).

RESULTS

Among 19,385 deliveries at our institution during the total study period (January 2009 to December 2020), the prevalence of symptomatic congenital CMV infection was estimated to be 0.15% (n = 30).

Clinical characteristics of prenatal period

As summarized in **Table 1**, median maternal age was 31 years and parous women accounted for 65.5% of the sample. Median gestational age at delivery was 32.2 weeks (22.6–40.0). Among 29 mothers, 19 (65.5%) delivered preterm (< 37 weeks). Among them, spontaneous preterm delivery occurred in 11 cases (57.9%). The most common indication for preterm delivery was non-reassuring fetal heart rate (6/19; 31.6%), followed by chorioamnionitis (1/19; 5.3%)

Table 1. Maternal characteristics and prenatal USG findings in pregnancies with congenital CMV infection

Variables	Values
Maternal characteristics (n = 29)	
Maternal age, yr	31 [22–40]
Parous	19 (65.5)
GDM	3 (10.3)
Preeclampsia	4 (13.8)
Twin pregnancy[a]	1 (3.4)
Cesarean section	15 (51.7)
Gestational age at delivery, wk	32.4 [22.6–40.0]
Preterm delivery < 28 wk	9 (31.0)
Preterm delivery < 34 wk	17 (58.6)
Preterm delivery < 37 wk	19 (65.5)
Prenatal USG findings (n = 28)[b]	Infants with abnormality (%)
No abnormal findings	9 (32.1)[c]
Abnormal findings	19 (67.9)[c]
Fetal growth restriction	14 (50.0)[c]
Abnormal placenta (placentomegaly or calcification)	5 (17.9)[c]
Ventriculomegaly	5 (17.9)[c]
Ascites	3 (10.7)[c]
Echogenic bowel	3 (10.7)[c]
Pericardial effusion	2 (7.1)[c]
Hydrops	2 (7.1)[c]

Categorical statistics are expressed as number (percentage) and continuous data are expressed as median and range.
USG = ultrasonography, CMV = cytomegalovirus, GDM = gestational diabetes mellitus.
[a]Both babies had congenital CMV infections and were delivered at 32 complete weeks.
[b]Two cases were excluded because they were delivered before ultrasound examination, immediately after transfer to our institution.

and maternal severe preeclampsia (1/19; 5.3%). The most common abnormal sonographic finding was FGR (50%) followed by ventriculomegaly (17.9%) and abnormal placenta (17.9%) defined as thick placenta and calcification. Other abnormal sonographic findings included ascites (10.7%), echogenic bowel (10.7%), pericardial effusion (7.1%), and hydrops (7.1%). No abnormal prenatal sonographic findings were observed in one third of births.

Fig. 1 depicts the flowchart of maternal CMV serology tests among cases of abnormal sonographic findings (n = 19). We found that only 8 mothers underwent maternal CMV serology test for IgM with or without IgG test during pregnancy and there were only 2 cases of positive or equivocal IgM, indicating very low rates of suspected primary infection.

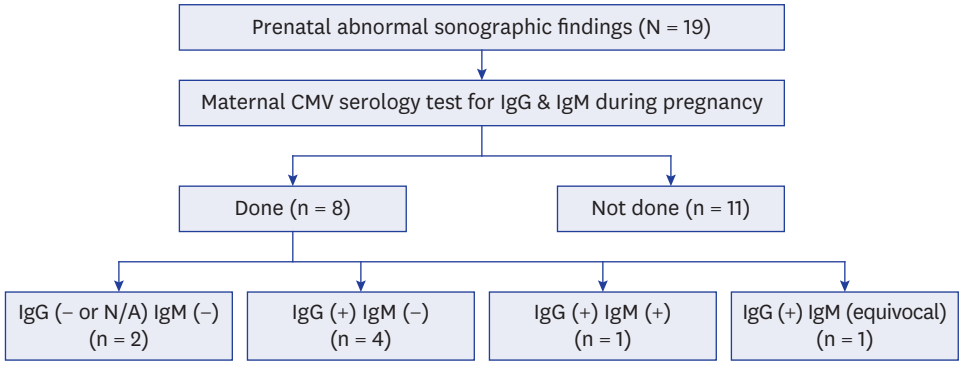

Fig. 1. Maternal CMV serology results among abnormal sonographic findings.
CMV = cytomegalovirus, N/A = not applicable.

https://doi.org/10.3346/jkms.2023.38.e249

Postnatal findings during neonatal period

Table 2 summarizes clinical and laboratory findings of infants with congenital CMV infections. Median birth weight was 1,395g [410–3,020]. The most common clinical manifestation of neonates with CMV infection was jaundice (58.6%), followed by ventriculomegaly (48.3%). Among laboratory findings, AST elevation (55.2%) and thrombocytopenia (51.7%) were observed in about half of the subjects. The mortality rate of our CMV cases was 16.7% (n = 5), all of them occurred in extreme preterm birth (range 22.6–26.3 weeks). In detail, three of them died for pulmonary hypertension, and the other two died due to complications from tension pneumonia and extremely low birth weight. Only infants with moderate to severely symptomatic congenital CMV disease were treated, while mildly symptomatic patients were followed without treatment. Infants with moderate to severely symptomatic congenital CMV disease were identified when they showed more than one of the following symptoms and signs: low platelet count, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, elevated liver enzymes or total bilirubin, chorioretinitis, CMV DNA detection in cerebrospinal fluid, microcephaly, radiographic abnormalities of the central nervous system such as ventriculomegaly, intracerebral calcifications, periventricular echogenicity, and cortical or cerebellar malformations.[6] In our study, 56.7% (17/30) of the congenital CMV infants received antiviral treatment with ganciclovir or valganciclovir in 15 and 8 cases, respectively. Six infants were treated with ganciclovir followed by valganciclovir. Six out of 14 infants who received anti-viral treatment with long term outcome available were found to have developmental delays, whereas 4 out of 9 cases who were followed without treatment showed developmental delays (42.9% vs. 44.4%; $P = 1.000$). Hearing loss were observed in 8 out of 14 individuals who got anti-viral treatment and in 1 out of 7 cases that were followed without treatment (57.1% vs. 14.3%; $P = 0.161$). These results suggest that patients with moderate to severely symptomatic congenital CMV disease could have similar long-term outcomes with mildly symptomatic infants by the proper anti-viral treatment.

Placental histologic findings

Table 3 summarizes detailed placental findings of congenital CMV infection. The most common histologic finding was chronic villitis (66.7%) followed by calcification (63.0%) and delayed maturation (37.0%). Of note, viral inclusions by CMV were identified in only six cases (22.2%).

Table 2. Clinical and laboratory findings of infants with congenital cytomegalovirus infection

Clinical and laboratory findings (N = 30)	Values
Clinical findings	
Male	14 (46.7)
Birth weight, g	1,395 [410–3,020]
Less than 1,000 g	10 (33.3)
1,000 g to 1,500 g	6 (20.0)
1,500 g to 2,500 g	10 (33.3)
2,500 g or more	4 (13.3)
Jaundice	17/29 (58.6)
Ventriculomegaly	14/29 (48.3)
Small for gestational age	14 (46.7)
Microcephaly	9/26 (34.6)
Seizure	7/29 (24.1)
Death	5 (16.7)
Retinitis	3/26 (11.5)
Intracranial calcification	3/29 (10.3)
Laboratory findings	
Aspartate aminotransferase elevation > 40 U/L	16/29 (55.2)
Thrombocytopenia, platelet count < 100,000/mm^3	15/29 (51.7)

Categorical statistics are expressed as number (percentage) and continuous data are expressed as median and range.

https://doi.org/10.3346/jkms.2023.38.e249

Table 3. Placental findings of congenital CMV infection

Placental findings (N = 27)[a]	Values
Abnormal placental findings	26 (96.3)
Villitis	18 (66.7)
Calcification	17 (63.0)
Delayed maturation	10 (37.0)
Acute chorioamnionitis	9 (33.3)
Hemosiderin	9 (33.3)
Plasma cells	8 (29.6)
Stromal fibrosis	8 (29.6)
Funisitis	7 (25.9)
Viral inclusions	6 (22.2)
Chorionic vasculitis	2 (7.4)

Categorical statistics are expressed as number (percentage).
CMV = cytomegalovirus.
[a]We excluded three cases of congenital CMV infection for which the placenta was not examined histologically after delivery.

Table 4. Long term neurologic outcomes and hearing loss of infants with congenital cytomegalovirus infection

No.	Gestational age at delivery, wk	Birth weight, g	Abnormal placental findings	Viral inclusion	Antiviral treatment	Developmental delay[a]	Neonatal hearing screening test	Hearing loss[b]	Death
1	32+3	1,582	+	-	+	+	+	+	-
2	38+5	2,700	+	-	-	- and N/A[c]	-	-	-
3	38+1	2,210	N/A	N/A	+	-	-	+	-
4	23+3	580	+	-	+	+	+	-	-
5	37+3	1,860	+	+	+	-	-	-	-
6	37+3	1,976	+	-	-	-	-	N/A	-
7	25+1	860	+	-	-	-	-	-	-
8	30+5	1,090	-	-	-	-	-	-	-
9	40+0	3,020	N/A	N/A	+	-	+	+	-
10	23+0	500	+	-	-	+	+	-	-
11	35+0	1,840	+	-	+	-	-	-	-
12	37+0	1,380	+	-	+	+	+	+	-
13	27+4	820	+	-	+	-	+	+	-
14	26+2	840	+	+	+	N/A	N/A	N/A	+
15	24+1	610	+	-	-	N/A	N/A	N/A	+
16	37+5	2,240	+	-	+	N/A	+	N/A	-
17	37+4	2,000	+	-	+	-	-	+	-
18	33+0	2,410	+	-	-	+	-	+	-
19	30+2	1,410	+	-	+	+	-	-	-
20	36+5	2,290	+	-	+	+	-	+	-
21	22+4	490	+	-	-	N/A	N/A	N/A	+
22	25+5	860	+	-	-	N/A	N/A	N/A	+
23	32+0	640	+	+	-	+	-	-	-
24	32+0	1,190	+	+	-	+	-	-	-
25	33+4	1,900	+	-	+	-	-	-	-
26	25+4	410	+	-	-	N/A	N/A	N/A	+
27	28+0	1,050	+	-	+	N/A	N/A	N/A	-
28	28+6	1,030	+	+	+	+	-	+	-
29	38+5	2,750	+	+	+	-	-	-	-
30	38+6	2,680	N/A	N/A	-	-	-	N/A	-
Total (%)			26/27 (96.3)	6/27 (22.2)	17/30 (56.7)	10/23 (43.5)	7/24 (29.2)	9/21 (42.9)	5/30 (16.7)

N/A = not applicable.
[a]Clinically assessed by pediatricians or rehabilitation physicians at least 1 year of age and/or by Denver II or Bayley II/III tests within 3 years of age.
[b]Assessed after 1 year age.
[c]Reached normal developmental milestones at 2 month of age when clinically assessed by pediatricians, but no further data were available due to follow up loss.

Long-term neurologic outcomes and hearing loss with follow up

Table 4 summarizes long-term neurologic outcomes and hearing loss of infants with congenital CMV infection. Among cases with complete information available about hearing after 1 year of age, hearing loss was confirmed in 42.9% (9/21) during the follow-up period.

https://doi.org/10.3346/jkms.2023.38.e249

Developmental delay was confirmed in 43.5% of infants (10/23), and among these 3 infants were less than 1 kg birth weight. At least 3 of the 6 cases in which viral inclusions were identified in the placenta were found to have developmental delays in long-term outcomes, however, only 7 of the 21 cases without viral inclusions were confirmed to have developmental delays (50.0% vs. 33.3%; $P = 0.638$). Regarding hearing loss, 1 of 6 cases in which viral inclusions were identified in the placenta were found to have hearing loss, however, 6 of 21 cases without viral inclusion were confirmed as hearing loss (16.7% vs. 28.6%; $P = 1.000$).

DISCUSSION

Our data showed that the birth prevalence of symptomatic congenital CMV infection was 0.15% in our institution, which was lower than the global congenital CMV prevalence at live birth of 0.7%.[1,2] Each year, 0.5 to 1.0% of all newborns in the United States are born with congenital CMV infection,[18] and about 0.37% in France.[19] According to a recent Japanese cohort study that included universal neonatal screening, the incidence of congenital CMV at a university hospital (0.69%) was higher than in a primary maternity hospital (0.23%, $P < 0.01$).[20] In contrast, our cases of congenital CMV were mostly derived from symptomatic CMV based on clinical suspicion of congenital CMV infection in either the prenatal or postnatal period rather than results of universal screening. In this point, we may underestimate the prevalence of congenital CMV. However, as this study was conducted at a single tertiary institution in Korea where high-risk pregnant women with symptomatic congenital CMV infection are more likely to be admitted, the incidence of congenital CMV infection may be overestimated in regard to the national prevalence.

In general, obstetric suspicion of fetal CMV infection generally occurs based on prenatal ultrasound findings suspicious of viral infection. In our cohort, the most common prenatal ultrasound finding was FGR (50%) followed by ventriculomegaly (17.9%) and abnormal placenta (17.9%). This is consistent with previous review studies, which described the prevalence of ultrasound findings for CMV infection including echogenic bowel (4.5–13%), ventriculomegaly (4.5–11.6%), cerebral calcification (0.6–17.4%), and FGR (1.9–13%).[21] Ultrasound image abnormalities were identified in less than 50% of congenitally CMV infected fetuses.[6,21] Similarly, in our study, one third of CMV cases had no abnormal prenatal sonographic findings. Collectively, these results suggest that normal prenatal ultrasounds cannot exclude congenital CMV infection.

At present, routine screening for CMV infection during pregnancy is not recommended, because a clear understanding of disease processes is lacking and early interventions that can change the course of the disease have not been validated.[21] However, most healthy women who acquire CMV infections, especially non-primary type infections, during their pregnancy are asymptomatic or have only flu-like symptoms that are not specific to CMV.[4] It is hard to suspect congenital CMV infection during pregnancy only with maternal symptoms or signs. Therefore, it is important not to miss any clues indicating congenital CMV, such as prenatal ultrasound findings and postnatal clinical and laboratory findings.

When congenital CMV infection is highly suspected, the best option for prenatal diagnosis is amniocentesis after 21 weeks of gestation and 6 weeks after maternal primary infection.[21] However, in our cohort, there was no case in which congenital CMV infection was prenatally diagnosed through amniocentesis. In this study, only 8 women underwent maternal CMV

https://doi.org/10.3346/jkms.2023.38.e249

serology tests for IgM with or without IgG tests during their pregnancy, who had abnormal prenatal ultrasound findings. Among them, there was only one case (12.5%) with positive IgM during pregnancy. Therefore, it can be inferred that the possibility of congenital CMV infection due to maternal primary infection was very low in our cohort. In addition, because we did not perform the immunoglobulin avidity test for one case of equivocal IgM, it was impossible to accurately determine the rate of primary CMV infection during current pregnancies in our cohort. We can only deduce that the majority of congenital CMV infections in our cohort originated from seropositive women, which is consistent with the results of previous studies in high seroprevalence countries such as Brazil.[8,22] According to a recent population-based prediction model, about 57 to 96% of all congenital CMV infections occur in infants born to women with non-primary maternal infection during pregnancy in populations with population sero-positive prevalences of 30% to 95%.[8] In Korea, seropositivity for CMV infection is very high among women of childbearing age. Therefore, more focus on congenital CMV infections after non-primary maternal infection is required in Korea. It was also indicated that maternal type of infection (primary vs. non-primary) itself was not associated with neonatal symptom and long-term neurologic outcomes.[23]

Meanwhile, 2–3 weeks after birth, it is very difficult to distinguish congenital CMV infection from postnatally acquired CMV infection by serological methods.[18,24] Therefore, it is important to detect and perform diagnostic tests for neonates at high risk for congenital CMV infection during the prenatal period or the first 2–3 weeks of life to establish future treatment directions and follow-up plans.[18] Early suspicion and diagnosis of hearing loss allow for better outcomes in children with CMV-related SNHL.[4]

So far, there are no proven therapies to prevent vertical transmission of CMV during pregnancy or treat congenital CMV infected fetuses in utero.[21] Some previous clinical trials showed effectiveness of antenatal treatment for congenital CMV infection to prevent maternofetal transmission or to reduce the viral burden in infected fetuses.[25-27] Ganciclovir and its oral prodrug valganciclovir are the most effective treatments for CMV infection currently available, but because of its extremely high *in vitro* genotoxicity, they have been labeled potentially teratogenic.[22] Acyclovir and its prodrug valaciclovir are other well-known DNA-polymerase inhibitors. A previous clinical study has demonstrated the therapeutic efficacy of high dose valaciclovir in preventing CMV infection in transplant recipients.[28] Compared to ganciclovir, valacyclovir is less effective for preventing viral reproduction in CMV infection, but are neither genotoxic nor carcinogenic in vitro or in animals.[22] Also, a French study reported efficient placental transfer of valaciclovir, that it is concentrated in the amniotic fluid with no accumulation.[26] Administration of valaciclovir 8g/day orally during pregnancy to mothers whose fetal infections were confirmed by amniocentesis resulted in larger proportions of asymptomatic newborns (82%; range 67–88) than in an untreated historical cohort (43%; range 29–57).[25-27] Therefore, in cases of confirmed congenital CMV infection amniocentesis, particularly in symptomatic cases, maternal therapy with valacyclovir during pregnancy can be recommended after parent counselling. Early treatment of pregnant women with primary infection may prevent termination of pregnancies or delivery of infants with congenital CMV infection, while additional evidence about secondary infection is required.[25,29]

The placenta is the main route for vertical transmission of CMV during pregnancy.[16] In our study, all placentas were reviewed and reassessed by a single pathologist (JSK) to evaluate placental histologic findings, which can be associated with congenital CMV infection. Chronic villitis (66.7%) was the most common finding, although it is not specific for congenital CMV

https://doi.org/10.3346/jkms.2023.38.e249

infection. Among specific findings, viral inclusions by CMV were observed in only 6 cases (22.2%) in our study, which was much lower than in a previous Japanese study showing the presence of intranuclear viral inclusions in about half of congenital CMV infections.[16]

Of note, in our study, we also correlated placenta histology with long-term neurologic outcomes. Even though differences in long-term outcomes according to abnormal findings including viral inclusion were not found to be statistically significant, there was a tendency toward neurologic impairment in the viral inclusion-positive cases. In a previous study, the presence of intranuclear inclusions was not significantly different according to the presence of symptoms of congenital CMV infection or maternal infection type (primary or non-primary),[16] and there was no association between viral inclusion in the placenta and neurologic impairment. Given that the prediction of long-term outcomes including SNHL is currently limited in clinical practice, further analysis of the relationships between detailed placental pathology in congenital CMV infections and neurologic outcomes, which include quantitative measurements of viral load using real time PCR in placental tissue, in a larger cohort is necessary.

In Korea, all neonates receive routine screening for hearing loss via automated OAE or AABR tests after birth[30-32] A Korean government-supported newborn hearing pilot project was started in 2007[9] and routine screening has been covered by national insurance since 2018.[32] However, a normal newborn hearing screening test result is not sufficient to rule out hearing loss associated with congenital CMV infection, because 10-15% of children who are asymptomatic at birth will eventually develop hearing impairment.[4,33,34] For this reason, we evaluated hearing ability not only by automated OAE of AABR tests after birth but also hearing test results evaluated by an otolaryngologist after 1 year of birth. The prevalence of hearing loss in our cohort was 42.9% (9/21) during the follow-up period. In fact, congenital CMV infection is the most common non-genetic cause of congenital SNHL.[35] Clinical spectra of hearing loss associated with CMV infection vary from mild to severe.[36] Hearing loss may not be present at birth but later progression or fluctuation of hearing have been noted.[37,38] Recent study conducted in Korea proposed the clinical significance of CMV diagnostic test after 3 weeks from birth in children with SNHL.[39] However, the clinical utility of diagnostic strategy is needed to be examined in further research. In order to evaluate developmental delay, the judgment of the rehabilitation physician and the results of Denver II or Bayley II/III tests were examined and developmental delay was confirmed in 43.5% of infants (10/23). In a 2013 study that explored long-term outcomes of congenital CMV infection at 5 years in Sweden and the United Kingdom, 18% of children with congenital CMV infection suffered developmental impairment. Symptomatic children exhibited noticeably greater neurological sequelae than asymptomatic children (42% vs. 14%, $P = 0.006$).[40]

The main strength of this study is that we analyzed the whole spectrum of disease at once through a multidisciplinary approach as a longitudinal study. However, in this retrospective study we included only data from a single center and did not compare congenital CMV infection cases with controls. To address these limitations, a prospective study recruiting mothers to prospectively assess the prevalence and risk factors of congenital CMV infection was started in 2020 and is currently underway at our institution.

Our results emphasize the importance of evaluating congenital CMV infection in Korea and of understanding the clinical manifestation by a multidisciplinary approach. Efforts are needed to reduce neurologic sequelae of congenital CMV infection through early

intervention by diagnosing disease without missing single clues during the prenatal period and immediately after birth. Congenital CMV infections have various spectra of signs that include multiple organ systems. Therefore, a multidisciplinary approach, including obstetrics, pediatrics, pathology, otolaryngology, and rehabilitation medicine, is critical for detecting congenital CMV. Also, further studies are needed to establish the cost-effectiveness of universal screening of congenital CMV infection.

REFERENCES

1. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007;17(4):253-76.
PUBMED | CROSSREF
2. Leruez-Ville M, Ville Y. Fetal cytomegalovirus infection. *Best Pract Res Clin Obstet Gynaecol* 2017;38:97-107.
PUBMED | CROSSREF
3. Choi SR, Kim KR, Son S, Kim DS, Chang YS, Cho EY, et al. The prevalence of symptomatic congenital cytomegalovirus disease in Korea; a 15-year multicenter study and analysis of big data from National Health Insurance System. *J Pediatric Infect Dis Soc* 2023;12(2):104-8.
PUBMED | CROSSREF
4. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. *Semin Perinatol* 2018;42(3):149-54.
PUBMED | CROSSREF
5. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol* 2007;17(5):355-63.
PUBMED | CROSSREF
6. Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis* 2017;17(6):e177-88.
PUBMED | CROSSREF
7. Yinon Y, Farine D, Yudin MH. No. 240-cytomegalovirus infection in pregnancy. *J Obstet Gynaecol Can* 2018;40(2):e134-41.
PUBMED | CROSSREF
8. de Vries JJ, van Zwet EW, Dekker FW, Kroes AC, Verkerk PH, Vossen AC. The apparent paradox of maternal seropositivity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model. *Rev Med Virol* 2013;23(4):241-9.
PUBMED | CROSSREF
9. Choi R, Lee S, Lee SG, Lee EH. Seroprevalence of CMV IgG and IgM in Korean women of childbearing age. *J Clin Lab Anal* 2021;35(4):e23716.
PUBMED | CROSSREF
10. Choi SR, Kim KR, Kim DS, Kang JM, Kim SJ, Kim JM, et al. Changes in cytomegalovirus seroprevalence in Korea for 21 years: a single center study. *Pediatr Infect Vaccine* 2018;25(3):123-31.
CROSSREF
11. Kim BJ, Han JJ, Shin SH, Kim HS, Yang HR, Choi EH, et al. Characterization of detailed audiological features of cytomegalovirus infection: a composite cohort study from groups with distinct demographics. *BioMed Res Int* 2018;2018:7087586.
PUBMED | CROSSREF
12. Kwak M, Yum MS, Yeh HR, Kim HJ, Ko TS. Brain magnetic resonance imaging findings of congenital cytomegalovirus infection as a prognostic factor for neurological outcome. *Pediatr Neurol* 2018;83:14-8.
PUBMED | CROSSREF
13. Grannum PA, Berkowitz RL, Hobbins JC. The ultrasonic changes in the maturing placenta and their relation to fetal pulmonic maturity. *Am J Obstet Gynecol* 1979;133(8):915-22.
PUBMED | CROSSREF
14. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. *Clin Infect Dis* 2013;57 Suppl 4:S178-81.
PUBMED | CROSSREF
15. Lim JS, Lim SW, Ahn JH, Song BS, Shim KS, Hwang IT. New Korean reference for birth weight by gestational age and sex: data from the Korean Statistical Information Service (2008–2012). *Ann Pediatr Endocrinol Metab* 2014;19(3):146-53.
PUBMED | CROSSREF

16. Uenaka M, Morizane M, Tanimura K, Deguchi M, Kanzawa M, Itoh T, et al. Histopathological analysis of placentas with congenital cytomegalovirus infection. *Placenta* 2019;75:62-7.
PUBMED | CROSSREF

17. Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015;372(10):933-43.
PUBMED | CROSSREF

18. Ross SA, Boppana SB. Congenital cytomegalovirus infection: outcome and diagnosis. *Semin Pediatr Infect Dis* 2005;16(1):44-9.
PUBMED | CROSSREF

19. Leruez-Ville M, Magny JF, Couderc S, Pichon C, Parodi M, Bussières L, et al. Risk factors for congenital cytomegalovirus infection following primary and nonprimary maternal infection: a prospective neonatal screening study using polymerase chain reaction in Saliva. *Clin Infect Dis* 2017;65(3):398-404.
PUBMED | CROSSREF

20. Yamada H, Tanimura K, Fukushima S, Fujioka K, Deguchi M, Sasagawa Y, et al. A cohort study of the universal neonatal urine screening for congenital cytomegalovirus infection. *J Infect Chemother* 2020;26(8):790-4.
PUBMED | CROSSREF

21. Hughes BL, Gyamfi-Bannerman C; Society for Maternal-Fetal Medicine (SMFM). Diagnosis and antenatal management of congenital cytomegalovirus infection. *Am J Obstet Gynecol* 2016;214(6):B5-11.
PUBMED | CROSSREF

22. Leruez-Ville M, Foulon I, Pass R, Ville Y. Cytomegalovirus infection during pregnancy: state of the science. *Am J Obstet Gynecol* 2020;223(3):330-49.
PUBMED | CROSSREF

23. Maltezou PG, Kourlaba G, Kourkouni E, Luck S, Blázquez-Gamero D, Ville Y, et al. Maternal type of CMV infection and sequelae in infants with congenital CMV: systematic review and meta-analysis. *J Clin Virol* 2020;129:104518.
PUBMED | CROSSREF

24. Lazzarotto T, Guerra B, Lanari M, Gabrielli L, Landini MP. New advances in the diagnosis of congenital cytomegalovirus infection. *J Clin Virol* 2008;41(3):192-7.
PUBMED | CROSSREF

25. 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. *Lancet* 2020;396(10253):779-85.
PUBMED | CROSSREF

26. Jacquemard F, Yamamoto M, Costa JM, Romand S, Jaqz-Aigrain E, Dejean A, et al. Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection. *BJOG* 2007;114(9):1113-21.
PUBMED | CROSSREF

27. Leruez-Ville M, Ghout I, Bussières L, Stirnemann J, Magny JF, Couderc S, et al. In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. *Am J Obstet Gynecol* 2016;215(4):462.e1-10.
PUBMED | CROSSREF

28. Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. *N Engl J Med* 1999;340(19):1462-70.
PUBMED | CROSSREF

29. Faure-Bardon V, Fourgeaud J, Stirnemann J, Leruez-Ville M, Ville Y. Secondary prevention of congenital cytomegalovirus infection with valacyclovir following maternal primary infection in early pregnancy. *Ultrasound Obstet Gynecol* 2021;58(4):576-81.
PUBMED | CROSSREF

30. Chung YS, Oh SH, Park SK. Results of a government-supported newborn hearing screening pilot project in the 17 cities and provinces from 2014 to 2018 in Korea. *J Korean Med Sci* 2020;35(31):e251.
PUBMED | CROSSREF

31. Korean Audiological Society, Korean Otologic Society. *Korean Clinical Practice Guideline: Newborn Hearing Screening 2010*. Seoul: ML Communications; 2011, 1-80.

32. Park SK, Chang J, Im GJ, Ahn JH, Lee JH, Han KD, et al. Status of early hearing detection and intervention in South Korea: a nationwide population-based study of national infant health checkup. *Sci Rep* 2020;10(1):16838.
PUBMED | CROSSREF

33. Nicloux M, Peterman L, Parodi M, Magny JF. Outcome and management of newborns with congenital cytomegalovirus infection. *Arch Pediatr* 2020;27(3):160-5.
PUBMED | CROSSREF

34. Pesch MH, Kuboushek K, McKee MM, Thorne MC, Weinberg JB. Congenital cytomegalovirus infection. *BMJ* 2021;373(1212):n1212.
PUBMED | CROSSREF

35. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. *Clin Microbiol Rev* 2013;26(1):86-102.
PUBMED | CROSSREF

36. Foulon I, Naessens A, Faron G, Foulon W, Jansen AC, Gordts F. Hearing thresholds in children with a congenital CMV infection: a prospective study. *Int J Pediatr Otorhinolaryngol* 2012;76(5):712-7.
PUBMED | CROSSREF

37. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol* 2000;11(5):283-90.
PUBMED | CROSSREF

38. Kim JH, Roh KJ, Nam GS, Son EJ. Audiologic status of children with confirmed cytomegalovirus infection: a case series. *J Korean Med Sci* 2020;35(30):e244.
PUBMED | CROSSREF

39. Lee SY, Jeon HW, Ahn SY, Oh SH, Kim BJ, Choi BY. Significance of cytomegalovirus tests after three weeks of life in children with hearing loss. *Int J Pediatr Otorhinolaryngol* 2023;168:111555.
PUBMED | CROSSREF

40. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. *Clin Infect Dis* 2013;56(9):1232-9.
PUBMED | CROSSREF