

Original Article

Maternal transmission, neonatal outcomes, and predictors of adverse effects in congenital cytomegalovirus infection

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ABSTRACT

Background: Congenital cytomegalovirus (cCMV) infection, caused by a DNA beta-herpesvirus, is the most common congenital infection globally, with significant neurodevelopmental and audiological sequelae. This study aimed to evaluate maternal-to-fetal transmission rates, neonatal outcomes, and the predictive value of clinical and virological markers for adverse outcomes.

Methods: This prospective longitudinal study enrolled 43 neonates born to mothers with CMV infection during pregnancy (2019–2023). cCMV was diagnosed by CMV DNA detection in urine or saliva within the first two weeks of life. Neuroimaging, audiological evaluations, and neurodevelopmental assessments were conducted during follow-up. Statistical analyses examined associations between maternal infection type, neonatal findings, and clinical outcomes.

Results: Among 43 neonates, 31 (72%) were diagnosed with cCMV. Primary maternal infection was significantly associated with higher transmission rates ($p < 0.01$). Twelve infected infants (38.7%) showed neurological symptoms, most commonly of speech and motor delay. SNHL was diagnosed in 2 patients (6.4%). High blood viral load was significantly associated with adverse audiological outcomes ($p < 0.05$), while intrauterine growth restriction (IUGR) predicted adverse neurological outcomes ($p = 0.05$). No statistically significant association was found between MRI abnormalities and neurological or audiological outcomes, although a trend toward correlation with adverse outcomes was observed.

Conclusions: cCMV carries a high risk of neurodevelopmental and auditory sequelae. High blood viral load and IUGR may serve as early predictors of poor outcomes. Early diagnosis, parental counseling, and long-term follow-up remain essential. Larger multicenter studies are needed to validate these findings and refine predictive models.

1. Introduction

Congenital cytomegalovirus (CMV) infection, caused by a DNA beta-herpesvirus, is the most common congenital infection worldwide, with seroprevalence ranging from 40% to 80% in industrialized countries and higher rates in developing regions, which is influenced by geographic, socioeconomic, and ethnic factors [1,2]. Humans are the only reservoir

for this species-specific virus, which is transmitted via direct contact with bodily fluids such as saliva, urine, blood, genital secretions, or breast milk [3]. Pregnant women, particularly those employed in high-risk occupations like education and healthcare, are vulnerable due to frequent exposure to children's bodily fluids [4]. Primary maternal infection during pregnancy poses the highest risk of vertical transmission, with transmission rates ranging from 20% in the first trimester

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to as high as 70% in later trimesters [4–8]. Non-primary infections—reactivation or reinfection in seropositive women—also contribute significantly to congenital infections, though their transmission dynamics are less well defined [9,10]. Despite maternal seropositivity, transmission and symptomatic disease can still occur, reflecting the complex interaction between maternal immunity, viral strain, and fetal susceptibility (see Fig. 1).

Due to the absence of a CMV vaccine, preventive strategies remain essential. Hygiene measures—including handwashing, avoiding sharing utensils, and limiting kissing on the mouth—are widely recommended [11]. International health bodies such as the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) stress the importance of behavioral interventions and prenatal counseling in reducing risk [12,13]. Nevertheless, these measures are underutilized in standard prenatal care, contributing to low maternal awareness and persistent CMV transmission [14].

Approximately 10–15% of neonates with congenital CMV (cCMV) are symptomatic at birth, with clinical signs such as petechiae, hepatosplenomegaly, jaundice, or microcephaly. Central nervous system (CNS) involvement is common and correlates with poor neurodevelopmental outcomes, including sensorineural hearing loss (SNHL), which affects 30–65% of symptomatic and 7–15% of asymptomatic infants [2,15]. Importantly, SNHL may present late or progress, underscoring the need for long-term monitoring [16].

Neonatal diagnosis relies on PCR testing of saliva or urine within the first three weeks of life. Saliva PCR, with high sensitivity and specificity, is preferred for its ease of collection, though precautions are necessary to avoid contamination with breast milk [17]. Management involves antiviral therapy, valganciclovir or ganciclovir, for symptomatic cases. Treatment within the first month of life aims to prevent CNS and auditory damage, with duration varying from six weeks to six months based on disease severity [18].

Routine follow-up involves serial audiological testing, neuroimaging, and developmental assessments to monitor long-term outcomes [19]. Universal newborn screening for CMV, despite its potential to enable timely interventions, remains underutilized: saliva PCR is a feasible screening method due to its sensitivity and parental acceptability [20].

This study aimed to evaluate the clinical characteristics, transmission rates, and long-term outcomes of neonates born to mothers with CMV infection during pregnancy, with a specific focus on vertical transmission rates, neurodevelopmental and audiological sequelae, and the potential predictive value of neonatal findings. By analyzing maternal infection timing and type, alongside postnatal assessments, this study seeks to identify key factors influencing prognosis and inform strategies for improved management and follow-up of affected infants.

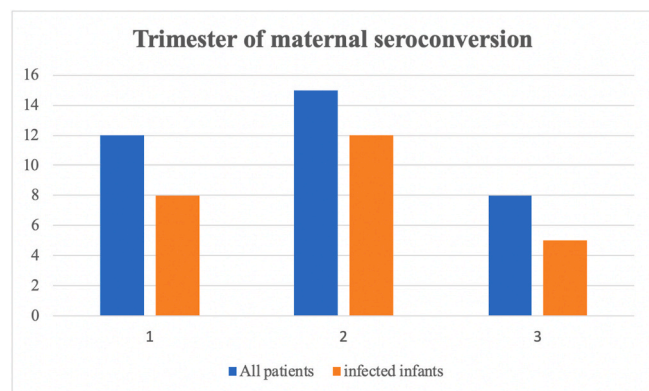


Fig. 1. Trimester of maternal seroconversion in all the patients enrolled and the sample of congenitally infected infants.

2. Patients and methods

This prospective longitudinal observational study was conducted at Policlinico-San Marco University Hospital, a major tertiary care center in Catania, Sicily, from 2019 to 2023. The study aimed to evaluate the clinical, neurodevelopmental, and audiological outcomes in neonates born to mothers with confirmed CMV infection during pregnancy. Neonates were enrolled consecutively, provided they met the inclusion criteria and their families consented to participate in the research. The follow-up period extended to at least two years, ensuring comprehensive longitudinal data on developmental and clinical trajectories.

Inclusion criteria required evidence of maternal CMV infection during pregnancy, diagnosed through serological and virological analyses. Neonates who had previously undergone genetic screening (e.g., chromosomal microarray analysis or targeted gene panels) and tested positive for pathogenic variants were excluded from the study.

2.1. Maternal infection: definitions and diagnostics

Maternal CMV infection was classified into two distinct categories based on clinical and serological findings.

- 1. Primary CMV Infection:** Diagnosed in seronegative pregnant women who seroconverted during pregnancy. This was confirmed by detecting CMV-specific IgM antibodies and the subsequent emergence of CMV-specific IgG antibodies. Repeat serological tests conducted 10–15 days after initial detection were critical for confirmation.
- 2. Non-Primary CMV Infection:** Defined as reactivation or reinfection in seropositive women. This was indicated by a ≥ 4 -fold rise in CMV-specific IgG titers and/or CMV-specific IgM detection. Maternal body fluid analysis, including blood and urine CMV DNA detection, provided additional diagnostic support.

2.2. Definition and diagnosis of congenital CMV (cCMV)

cCMV was confirmed in neonates by detecting CMV DNA in urine or saliva collected within the first two weeks of life using PCR-based methods.

Infection was classified as symptomatic if neonates exhibited one or more of the following clinical or laboratory features, based on the consensus definition by Rawlinson et al. [21].

- Intrauterine Growth Restriction (IUGR): Birth weight below -2 SD for gestational age
- Microcephaly: Head circumference below -2 SD for gestational age
- Central nervous system (CNS) involvement: seizures, abnormal neuroimaging (e.g., calcifications, cysts, ventriculomegaly), or hypotonia with structural abnormalities
- Sensorineural hearing loss (SNHL) confirmed by ABR
- Chorioretinitis
- Petechiae
- Thrombocytopenia: platelet count $< 100,000/\text{mm}^3$
- Hepatitis: ALT > 100 U/L or direct bilirubin > 3 mg/dL

2.3. Viral load assessment

We defined a high CMV viral load in urine as $> 10,000,000$ IU/ml, consistent with values reported in newborns with congenital CMV infection [1–3]. In blood, a threshold of 3500 genome equivalents/ml (gEq/ml) was used to stratify patients based on viremia levels, as this value has been previously associated with a higher risk of adverse audiological outcomes [22].

2.4. Neuroimaging protocols

Brain ultrasound (US) served as the primary imaging modality for detecting structural brain abnormalities. Examinations were conducted by neonatologists and radiologists experienced in neonatal imaging. Abnormal findings included lenticulostriate vasculopathy (LSV), periventricular cysts, calcifications, cystic periventricular leukomalacia (PVL), ventriculomegaly, and vermis hypoplasia. Advanced imaging using magnetic resonance imaging (MRI) was performed when US findings warranted further investigation or when neurological symptoms suggested potential structural anomalies. MRI findings were categorized using Alarcon's scoring system, which ranges from minor abnormalities (score 1) to severe malformations (score 3).

2.5. Audiological and neurological assessments

Audiological assessments involved otoacoustic emissions (OAE) and auditory brainstem responses (ABR) performed at birth. Follow-up evaluations were conducted every six months until two years of age, then annually. Neurological assessments focused on motor, cognitive, and behavioral outcomes. Pediatric neurologists evaluated neonates at baseline, three months, six months, one year, 18 months, and two years, with additional assessments scheduled as needed for complications such as seizures or developmental delays.

2.6. Antiviral therapy

Infected neonates were considered for antiviral therapy if they presented with at least one major criterion of central nervous system (CNS) involvement (e.g., microcephaly, neuroimaging abnormalities, or seizures) or confirmed sensorineural hearing loss (SNHL) based on ABR testing. Treatment decisions followed published guidelines and were made after obtaining informed parental consent. Intravenous ganciclovir and oral valganciclovir were the primary antiviral agents used. Hematological monitoring was performed throughout the treatment to identify potential side effects, including neutropenia and anemia.

Not all patients fulfilling treatment criteria received antiviral therapy. The reasons included diagnosis beyond the neonatal period, parental refusal, comorbidities, or unavailability of treatment.

2.7. Statistical analysis

Due to the sample size ($n = 43$), non-parametric statistical methods were employed. Chi-square (χ^2) tests and odds ratios (OR) were used to analyze correlations between maternal, neonatal, and virological factors and clinical outcomes. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Study population

From 2019 to 2023, a total of 43 neonates born to mothers with confirmed CMV infection during pregnancy were enrolled in this longitudinal study. These neonates were identified either during the prenatal period, through maternal testing and fetal monitoring, or postnatally, based on clinical suspicion or universal screening protocols. Among these, 31 (72%) were diagnosed with congenital CMV (cCMV) infection. Diagnosis was confirmed by detecting CMV DNA in urine or saliva samples collected within the first two weeks of life. The remaining 12 neonates who tested negative for cCMV served as a comparison group to better understand factors influencing vertical transmission and clinical outcomes. The estimated annual incidence of cCMV in eastern Sicily was 0.05%, derived from regional birth data (20,203/year) and the average number of confirmed cases referred to our center. Importantly, 90% of the study population were enrolled in the first year of life, usually within the third month, and the others later.

Seroconversion occurred during the first trimester in 12 women (28%), second trimester in 15 (35%), and third trimester in 8 (19%). In 8 cases (18%) the timing was unknown. Transmission rates were: 66.7% (8/12) for first trimester, 80% (12/15) for second, and 62.5% (5/8) for third trimester seroconversions. Odds ratio (OR) analysis comparing these groups revealed no statistically significant difference in transmission rates (1st vs. 2nd trimester: OR = 0.191, $\chi^2 = 0.036$; 1st vs. 3rd trimester: OR = 0.779, $\chi^2 = 0.617$; 2nd vs. 3rd trimester: OR = 0.898, $\chi^2 = 0.829$).

Secondly, our interest was directed toward the type of maternal infection, which is primary or secondary infection. Eleven out of 18 pregnant women had a primary infection (61%); otherwise 7 of the totals showed a secondary infection (39%). In 25 cases, the type of infection could not be determined. An increased mother-to-child transmission rate after primary infection, if compared with secondary infection, was observed. The increase was statistically significant at a level better than 1% (OR = 2.399, $\chi^2 = 7.481$). Therefore, women with primary infection have a higher probability to give birth to infected newborns than mothers with secondary infection. The same sample of patients was used to study the correlation between the type of maternal infection and the appearance of symptoms of CMV disease in infected infants (OR = 0.261, $\chi^2 = 0.069$). In this case no correlation could be established.

In the present study, only 5 pregnant women underwent amniocentesis, and 3 of them resulted positive. The viral load in amniotic fluid was also considered. It was high in 1 case, and low in the other two. A correlation between viral load and postnatal outcome was not investigated because of the paucity of data. Currently, the child born from a mother with high viral load in amniotic fluid is one year old and has not yet had neurodevelopmental sequelae.

As concerns congenitally infected newborns, Table 1 summarizes important demographic, perinatal and clinical characteristics of the study patients. In the present sample, male and female were 49% and 51% respectively. No significant sex difference was observed (OR =

Table 1

Clinical and virological characteristics of the 31 newborns with congenital CMV infection. **Legend:** IUGR: intrauterine growth restriction; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; SNHL: sensorineural hearing loss. **Maternal seroconversion** was known for 35 mothers: ■ 1st trimester ($n = 12$): 8/12 infants infected (66.7%); ■ 2nd trimester ($n = 15$): 12/15 infants infected (80.0%); ■ 3rd trimester ($n = 8$): 5/8 infants infected (62.5%).

Characteristic	Value
Sex, n (%)	
Male	16 (52%)
Female	15 (48%)
Prematurity (≤ 37 weeks), n (%)	1 (3.2%)
First born, n (%)	14 (52%)
Birth anthropometrics	
Weight, mean (g)	3178
Weight, median (g)	3210
IUGR (< 3 rd centile), n (%)	2 (6.4%)
Head circumference, mean (cm)	33.9
Head circumference, median (cm)	34.0
Microcephaly, n (%)	4 (13%)
Perinatal factors	
Breastfeeding, n (%)	13 (52%)
Asphyxia, n (%)	1 (3.2%)
Virological findings	
CMV in saliva, n (%)	31 (100%)
CMV in urine, n (%)	31 (100%)
High viral load in urine ($> 10^7$ IU/ml), n (%)	14 (45%)
CMV in blood, n (%)	16 (51.6%)
Clinical findings	
Petechiae, n (%)	1 (3.2%)
Sensorineural hearing loss (SNHL), n (%)	2 (6.4%)
Chorioretinitis, n (%)	0 (0%)
Hepatitis (ALT > 100 U/L), n (%)	6 (19.3%)
Elevated GGT, n (%)	2 (6.4%)

0.095; $\chi^2 = 0.090$).

Newborns with CNS involvement—defined by neurological symptoms, neuroimaging abnormalities, or SNHL—were selected for therapy with intravenous ganciclovir or oral valganciclovir after informed consent from parents.

Four out of 31 infected newborns received antiviral treatment, 3 within the first year of life and 1 at 2 months old. In three cases ganciclovir was administered for one week and was followed by valganciclovir, and in the remaining case valganciclovir was used at the beginning. As concerns side effects, one case of transient anemia was observed. This resolved with folic acid therapy, without interruption of antiviral treatment. No other side effects were observed. Antiviral therapy was continued for six weeks in one case and for six months in two cases. The remaining one infant is still on treatment.

Table 2 shows the summary of data concerning antiviral treatment: time of starting, type of drug, duration of treatment, side effects and time of negativization of viremia. The characteristic of the participants to the treatment at baseline are summarized in Table 3.

3.2. Neurological outcome in symptomatic congenital CMV infection

3.2.1. Adverse neurological outcome

Neurological outcome was evaluated at the admission, at the 3rd month, 6th month, 1st year, 18th month and 2nd year of age. Three patients were enrolled after the second year of age.

The 38.7% ($n = 12$) of congenitally infected children manifested some neurological symptoms, during neonatal period or during the follow up. The most common observed clinical manifestation was speech delay (58.3%), followed by motor delay (50%), epilepsy (8.3%), microcephaly (8.3%) and behavior disorder (8.3%). In some instances, two symptoms coexisted, e.g., microcephaly and motor delay. No patients enrolled manifested signs of cerebral palsy or visual deficit. Table 4 summarizes neurological outcome in 12 symptomatic congenital CMV infected children. In the same table the maternal, neonatal and virologic characteristics of these 12 patients are summarized.

The age of onset of symptoms ranged from birth to the second year of age. Hypotonia and hypertonia were usually visible at birth, different from motor delay, which was usually diagnosed between the 6th month and 1st year of age when infants should reach their appropriate developmental milestones. Instead, the diagnoses of behavior disorder and speech delay were performed at least at the 2nd year of age. As regards epilepsy, only one patient experienced seizures characterized by sucking movements, hypertonia, and blinking, which is sometimes associated with perioral cyanosis. The age of onset of seizures was the first week of life and, after the performance of electroencephalography (EEG), the seizures required treatment with the antiepileptic drug levetiracetam. In our study population, 4 of the 12 patients with neurological manifestations had symptoms within the first month of life (33.3%), 4 within the first year (33.3%) and 4 within the second year (33.3%). In the present

Table 2

Details of antiviral treatment in four newborns with symptomatic congenital CMV infection.

Patient ID	Start of Treatment	GCV	ValGCV	Duration	Side Effects	Viremia Clearance
#1	2 nd month (Ongoing)	–	Yes	NA	NA	NA
#3	1st month	Yes	Yes	6 weeks	None	2 nd month
#8	1st month	Yes	Yes	6 weeks	None	2 nd month
#23	1st month	Yes	Yes	6 weeks	Anemia	3rd month

Legend: GCV: ganciclovir; ValGCV: valganciclovir; NA: not available/applicable. Patient #1 was still receiving treatment at the time of data cut-off; therefore, treatment duration, side effects, and time to viremia clearance were not yet evaluable.

study, no variation in age at symptom onset was observed.

3.3. Neuroimaging results

All congenitally infected infants enrolled within the first year of life underwent cranial US, except for 1 patient who underwent immediate MRI, to exclude cerebral stroke because of the sudden onset of seizures. The parents of the three patients enrolled after the second year of age did not have previous medical reports. Eleven patients underwent both US and MRI.

The most prevalent finding at brain US was lenticulostriate vasculopathy, observed in 6 of the 27 patients who underwent US (22.2%). Other abnormal findings were cystic periventricular leukomalacia in 1 patient (3.7%), periventricular cysts in 3 patients (11.1%) and cortical/subcortical calcifications (3.7%). One of these patients showed both a single calcification and lenticulostriate vasculopathy, and another both cystic periventricular leukomalacia (PVL) and brain calcifications.

Brain MRI abnormalities included single or multiple brain calcifications, caudothalamic germinolysis, periventricular cysts, cystic PVL and hyperintense WM. According to Alarcon score [23], 2 patients of 13 who underwent MRI (15.4%) had a score of “1”; otherwise 2 patients had a score of “3” (15.4%). Neither cortical malformation nor cerebellar hypoplasia was observed. In 9 of 13 patients, MRI did not reveal any significant abnormalities (69.2%) (Table 5).

When comparing MRI scores with Bayley-III composite scores in the cognitive, language, and motor domains, among the four patients with MRI abnormalities, all presented Bayley-III scores below 85 in at least one domain, and three had concurrent clinical neurological symptoms, including motor or language delay and epilepsy. In contrast, among the eight patients with normal MRI scans, four showed Bayley-III scores within the normal range (above 85) in all domains, while the other four had isolated borderline scores (between 70 and 85), most commonly in language development.

Although no formal multivariate adjustment was applied due to the limited sample size, these preliminary findings suggest that structural brain abnormalities identified by MRI may correlate with both clinical manifestations and poorer neurodevelopmental outcomes, as measured through objective standardized tools.

3.4. Predictive value of neonatal findings for neurological outcomes

In the present study, the association of 5 neonatal findings with neurological outcome was researched. The neonatal findings objects of the study were: grade 1–3 MRI anomalies, microcephaly, intrauterine growth restriction, urine and blood viral load. The aim of these tests was to search for some neonatal predictors of adverse neurological outcome.

In all, 13 patients underwent an MRI. Two of them showed an auditive sequela, three neurological symptoms and six other outcomes. Two patients had no outcome.

The OR and the χ^2 test cannot state a statistically significant correlation at a level of 5% between positive MRI and adverse neurological outcome (OR = 1.42 $\chi^2 = 2.24$).

Concerning IUGR, a comparison between two groups of newborns, small for gestational age and normal weight, was performed. A correlation between IUGR and adverse neurological outcome was observed, with a confidence level of 5% ($\chi^2 = 3.8$).

Concerning viral load, a discrimination between urine and blood viral load was necessary. At first, we selected newborns with high urine viral load at birth. The viral load was defined to be high when above 10,000,000 IU/ml. All 43 patients underwent CMV isolation in urine and 14 of them (45.1% of infected) had a high urine viral load at birth.

Attempts to correlate high urine viral load with general adverse outcomes, or, more specifically, with a negative neurological outcome, failed to give a positive result (for generic negative outcome OR = 1.133, $\chi^2 = 1.31$; for negative neurological outcome OR = 0.635, $\chi^2 = 0.406$).

Later, the correlation between blood viral load and adverse

Table 3

Clinical characteristics and treatment indications of patients who received antiviral therapy. Treatment indications were based on central nervous system involvement and/or confirmed SNHL, as per international recommendations. **Legend:** MRI: Magnetic Resonance Imaging; SNHL: Sensorineural Hearing Loss.

Patient ID	Gestational Age	Neurological Manifestations	MRI Findings	SNHL	Other Manifestations	Indication for Treatment
#1	Term	–	Multiple caudo-thalamic subependymal cysts	No	–	MRI abnormalities
#3	Term	–	–	Yes (severe unilateral)	–	Early-onset SNHL
#8	Term	Hypotonia	Periventricular cysts, frontal calcifications	Yes (mild unilateral)	Petechiae	SNHL + neurological signs
#23	Term	Seizures	Germinolysis of caudate nucleus and thalamus	No	–	Seizures + MRI abnormalities

neurological outcome was studied. Only 17 of 31 infected patients underwent dosage of CMV viral load in blood within the first month of life. Of them, 10 newborns had a positive result (58.8%), whereas in 7 cases the isolation of CMV in blood was negative. Also in this case, no statistical correlation between blood CMV detection and adverse neurological outcomes was found ($OR = 1.102$, $\chi^2 = 1.31$). A positive result was found linking the blood CMV detection and all the adverse outcomes. This correlation is established at a level better than 5% ($OR = 1.909$, $\chi^2 = 4.408$).

4. Sensorineural hearing loss in symptomatic congenital CMV infection

4.1. Adverse audiological outcome

All infected patients underwent both ABR and acoustic emissions, except for 3 patients enrolled after the first year of age. The results were normal in 25 patients (92.5%), whereas SNHL was diagnosed in 2 infants (7.5%).

Among infants with SNHL, one developed the disease within the first month of life, defined by specialists as severe and unilateral. During neonatal period, she did not have any neurological symptoms and neuroimaging (brain US and MRI) did not show any anomalies. Parents of the patient were informed about the risk of developing a progressive bilateral SNHL, so that an antiviral treatment with ganciclovir followed by valganciclovir was started (Table 2). Now the child is 27 months old. She has recently undergone audiological evaluation which showed a steadiness of inner ear damage. To date, neurodevelopmental evaluation has proven no further involvement of CNS, excluding inner ear involvement.

The second case concerns a male infant who manifested SNHL at 1 year old. Differently from the previous case, this patient had CNS involvement at birth, diagnosed at brain US and confirmed at MRI. This patient underwent an antiviral treatment with ganciclovir at first and valganciclovir thereafter, which continued for 6 weeks (Table 2). Moderate delay in lallation (12 months) and mild delay in ambulation (15 months) were observed, though the child now walks regularly and is able to pronounce phrases. The audiological assessment has not shown worsening of SNHL.

4.2. Predictive value of neonatal findings for audiological outcomes

We searched for neonatal predictors of adverse audiological outcome. In this case, we studied only 3 neonatal findings that could be associated with adverse audiological outcome: MRI score of 1–3, urine and blood viral load.

Unlike neurologic symptoms, SNHL was identified in only two patients, which likely explains why we found no statistically significant association between adverse neurological outcome and pathological MRI, high urine viral load and positive blood viral load.

Finally, assuming that a blood viral load of <3500 gEq/ml was associated with a lower risk of hearing loss in children born with

asymptomatic congenital infection, we tried to correlate blood viral load value (lower or higher than 3500 gEq/ml) with audiological manifestations. We observed a statistically significant association between high blood viral load (≥ 3500 gEq/ml) and adverse audiological outcome ($\chi^2 = 4.96$) although the sample of children with audiological manifestations in our study population was small.

5. Discussion

The relationship between gestational age and maternal-fetal transmission of CMV infection has been extensively studied, with most authors reporting an increased risk of transmission with advancing gestation [24–27]. Picone et al. analyzed maternal primary CMV infections in a cohort of 238 patients and they observed transmission rates of 36.5% in the first trimester, 40.1% in the second, and 65% in the third trimester [28]. However, our study did not demonstrate a statistically significant increase in transmission rates with advancing gestation. In our cohort, maternal-fetal transmission rates were 66.7%, 80%, and 62.5% for the first, second, and third trimesters, respectively. This discrepancy may reflect the smaller sample size of our study compared to larger cohorts in the literature. However, other contributing factors should be considered. First, differences in diagnostic protocols across centers—such as the use of PCR versus viral culture, or the timing and type of maternal serologic tests—may lead to variability in identifying maternal infection and congenital CMV. Second, follow-up protocols differ across studies. While some studies include systematic and long-term neurodevelopmental and audiological monitoring, others rely on short-term clinical observation, which may underestimate late-onset sequelae. Third, ethnic, genetic, and socioeconomic factors may influence both maternal immune response and fetal susceptibility to CMV, potentially altering transmission dynamics and clinical outcomes. In our cohort, regional characteristics of Eastern Sicily—including healthcare access, screening practices, and population-specific genetic predispositions—could have impacted the observed rates of infection and sequelae. These elements, taken together with sample size, may account for discrepancies between our findings and those reported in the literature.

Pregnant women are often most concerned about the risk of their child being symptomatic at birth. Previous studies have consistently shown that early gestational infection carries a higher risk of symptomatic congenital CMV and long-term sequelae. Pass et al. first demonstrated that maternal infection during the first trimester was significantly associated with CNS sequelae, particularly sensorineural hearing loss (SNHL) [29]. Later studies by Gindes et al. and Enders et al. found no symptomatic cases when maternal infection occurred in the third trimester [25,26]. Faure-Bardon et al. recently reinforced these findings, observing a 35% rate of sequelae in first-trimester infections compared to 0% in second- and third-trimester infections [30].

In our cohort, no statistically significant correlation between gestational age and symptomatic infection was observed. This discrepancy might be due to the limited follow-up in some cases and the lack of prenatal data for children enrolled later. These limitations hinder a

Table 4

Characteristics of 12 symptomatic congenital CMV infected children who manifested neurological symptoms. When the variable is not specified it was unknown. For “Antiviral treatment”, “refused” indicates that treatment was proposed in accordance with clinical guidelines but was declined by the parents after counseling. **Legend:** M: male; F: female; IUGR: Intrauterine Growth Restriction; US: ultrasound; MRI: Magnetic Resonance Imaging.

Patient #ID	Date of birth	Year of enrollment	Gender	Trimester of maternal seroconversion	Asphyxia	At term	IUGR	Microcephaly at birth	Neurological manifestation	Brain US	Brain MRI	Antiviral treatment	Bayley cognitive	Bayley language	Bayley motor
#1	April 22, 2023	2023	M	1st	No	Yes			-	Periventricular cysts	Multiple caudo-thalamic subependymal cysts	Yes	95	100	90
#6	December 13, 2022	2022	M	2nd	No	Yes	No	No	Poor eye contact	Lenticulostriated vasculopathy		Refused	100	95	100
#8	February 01, 2021	2021	M	1st	No	Yes	No	No	Hypotonia, psychomotor and speech delay	Periventricular cysts	Periventricular cysts, multiple periventricular frontal calcifications	Yes	70	65	80
#9	August 01, 2019	2022	F	2nd	No	Yes	No		Speech delay			No	85	75	85
#13	November 12, 2021	2022	M	2nd	No	Yes	Yes	Yes	Psychomotor delay	Normal		Yes	90	85	88
#18	January 06, 2021	2021	M	1st	No	Yes	No	No	Speech delay	Normal	Normal	No	90	92	94
#19	September 12, 2021	2021	F	2nd	No	Yes	Yes	No	Psychomotor and speech delay	Normal	Normal	No	88	85	87
#21	December 11, 2020	2020	M	1st	No	Yes	No		Speech delay	Normal		No	95	93	90
#22	February 25, 2018	2022	M	3rd	No	Yes	No	No	Speech delay			No	92	90	91
#23	February 21, 2022	2022	M	Unknow	No	Yes	No	No	Epilepsy		Caudo-thalamic germinolysis	Refused	75	70	72
#29	November 16, 2019	2021	M	Unknown	No	Yes			Behavior disorder		Normal	No	87	85	84
#31	June 28, 2022	2022	F	3	Yes	No	No	Yes	Microcephaly, motor delay	Periventricular cysts		Refused	80	78	75

Table 5
Neuroimaging results in infected newborns.

	Ultrasound (N = 27)		MRI (N = 13)	
	Normal	Abnormal (^a)	Normal	Abnormal
Total, n (%)	23 (85.2)	4 (14.8)	9 (69.2)	4 (30.8)
Normal neurological outcome, n (%)	18 (78.3)	1 (25)	6 (66.7)	1 (25)
Adverse neurological outcome, n (%)	5 (21.7)	3 (75)	3 (33.3)	3 (75)
Normal hearing, n (%)	22 (95.7)	3 (75)	8 (88.9)	3 (75)
SNHL, n (%)	1 (4.3)	1 (25)	1 (11.1)	1 (25)

Legend: MRI: Magnetic Resonance Imaging; SNHL: Sensorineural Hearing Loss.

^a Lenticulo-striated vasculopathy was not considered an abnormal ultrasound finding.

comprehensive understanding of the true relationship between gestational age and symptomatic outcomes.

CMV can be transmitted in utero during both primary and secondary maternal infections. Primary infections pose a much higher risk of vertical transmission, with rates ranging from 30% to 35%, compared to 1.1–1.7% for secondary infections [31–33]. Our findings align with this, showing a significant association between primary maternal infection and increased vertical transmission ($p < 0.01$). However, clinical outcomes did not differ significantly between primary and secondary infections, which was consistent with literature suggesting that secondary infections warrant the same careful monitoring to identify potential sequelae [34].

The study confirms that primary maternal infection during pregnancy is associated with a significantly higher rate of vertical transmission compared to secondary infections. This finding aligns with previous research and underscores the need for heightened awareness and targeted screening in pregnant women without preexisting immunity to CMV. Interestingly, while vertical transmission rates are higher in primary infections, our study did not find significant differences in the clinical manifestations of symptomatic cCMV between infants born to mothers with primary and secondary infections. This finding suggests that even secondary infections can lead to significant morbidity and they should not be underestimated.

The data also show that while vertical transmission rates tend to increase with gestational age at the time of maternal infection, the risk of symptomatic infection and adverse outcomes appears more strongly associated with first-trimester infections. However, our findings diverge from some of the literature, possibly due to the small sample size and variability in follow-up periods. This variability highlights the need for larger, multicenter studies to confirm these trends and improve our understanding of gestational timing's impact on fetal outcomes.

5.1. Neurodevelopmental outcomes and neonatal predictors

The classification of symptomatic and asymptomatic CMV infection varies widely across studies, leading to differences in reported prevalence. Rawlinson et al. proposed consensus definitions, categorizing symptomatic cases based on the severity and CNS involvement [22]. Approximately 10–15% of congenitally infected infants are symptomatic at birth, with half of these developing permanent sequelae. Among asymptomatic cases, 10–15% manifest late-onset symptoms [22].

In our study, 41.9% of infected neonates were symptomatic at birth, though this rate dropped to 19% when excluding transient liver enzyme elevations. Late-onset sequelae occurred in 28% of cases, which was higher than the 10% reported in the literature. This discrepancy may reflect our inclusion of mild motor and speech delays as symptomatic outcomes, which other studies might classify differently.

The role of neonatal findings such as brain MRI, microcephaly, intrauterine growth restriction (IUGR), and viral load in predicting neurodevelopmental outcomes has been a focus of research. Brain MRI

abnormalities, particularly cortical malformations, ventriculomegaly, and cerebellar hypoplasia, are strongly associated with poor outcomes [35]. While 13 infants in our cohort underwent MRI, only four showed abnormalities. Among these, two had adverse outcomes, while the others remained neurologically intact, highlighting the variability in prognosis even with abnormal imaging.

IUGR emerged as a significant predictor of poor neurological outcomes in our cohort, which was consistent with previous reports. From a pathophysiological perspective, IUGR is frequently associated with chronic uteroplacental insufficiency, resulting in reduced oxygen and nutrient delivery to the fetus. This compromised intrauterine environment can impair neuronal proliferation and migration during critical windows of brain development, predisposing to long-term cognitive and motor deficits. Furthermore, IUGR has been linked to increased risk of periventricular leukomalacia and altered brain connectivity, both of which are implicated in neurodevelopmental disorders [36,37]. In the context of congenital CMV, the overlap of viral cytopathic effects with a hypoxic milieu may compound neural injury, explaining the stronger association between IUGR and adverse neurological outcomes. These findings underscore the importance of monitoring fetal growth patterns as part of prenatal CMV management and risk stratification.

Microcephaly has been identified as a specific predictor of adverse outcomes, especially motor deficits. In our cohort, microcephaly was observed in 7.6% of symptomatic neonates and it was associated with motor delay. IUGR, another significant predictor, showed a strong correlation with adverse neurological outcomes, which was consistent with previous studies linking IUGR to fetal compromise and poor postnatal development [38].

High blood viral load has been shown to correlate with disseminated infection and adverse outcomes [39]. In our cohort, a positive association was observed between high blood viral load and overall sequelae, though this was not specific to neurological outcomes. Urine viral load, in contrast, showed no significant association with adverse outcomes, supporting earlier findings that blood load is a more reliable indicator of disease severity [40].

Our study evaluated multiple neonatal findings as potential predictors of adverse neurological outcomes, including microcephaly, intrauterine growth restriction (IUGR), and viral load. Among these, IUGR emerged as a significant predictor of poor neurological outcomes, suggesting its role as a marker of more severe in utero infection. Conversely, while blood viral load showed a correlation with overall adverse outcomes, no significant association was found with neurological outcomes specifically. Urine viral load, on the other hand, did not appear to correlate with either neurological or overall outcomes. These findings highlight the complexity of identifying reliable biomarkers and emphasize the need for a multifactorial approach to prognosis.

Neuroimaging findings, particularly brain MRI, were also explored as predictors of neurological outcomes. Despite the limited sample size, abnormalities on MRI were associated with a higher likelihood of adverse outcomes. However, the absence of statistically significant correlations in our cohort underscores the need for further research. Given MRI's ability to detect subtle abnormalities that are undetectable by ultrasound, it remains a valuable tool for assessing the extent of CNS involvement and guiding both counseling and treatment strategies.

5.2. Audiological outcomes and neonatal predictors

Congenital CMV infection is the leading non-genetic cause of SNHL, affecting approximately 33% of symptomatic and 10% of asymptomatic infants [41]. In our cohort, SNHL was observed in 8.3% of symptomatic and 3.2% of asymptomatic neonates. These rates are slightly lower than reported figures, which was likely due to the short follow-up period and small sample size. Progressive and delayed-onset hearing loss, common in congenital CMV, were observed in only one case.

However, this may underestimate the true burden of disease, as delayed-onset or progressive SNHL can manifest beyond early

childhood. Longer follow-up is essential to capture the full extent of audiological outcomes in these patients [42].

Abnormal neuroimaging findings are a recognized risk factor for SNHL. A recent study found a 42.9% risk of SNHL with abnormal imaging compared to 6.6% with normal results [43]. In our study, abnormal MRI findings were more common in children with SNHL, though statistical significance was not achieved. High blood viral load (≥ 3500 gEq/ml) was significantly associated with SNHL, which was consistent with previous studies demonstrating its predictive value [23].

Congenital CMV infection is well established as the leading non-genetic cause of SNHL in children, and our study reinforces this, with SNHL observed in both symptomatic and asymptomatic infants. The progression and delayed onset of SNHL, as noted in one of our cases, emphasizes the importance of long-term audiological follow-up. High blood viral load (≥ 3500 gEq/ml) emerged as a potential predictor of adverse audiological outcomes, aligning with previous studies that associate higher viral loads with increased risk of SNHL. However, the lack of correlation between urine viral load and audiological outcomes in our cohort suggests that blood viral load may be a more reliable marker for identifying infants at risk.

5.3. Antiviral treatment

Antiviral therapy has been shown to stabilize or improve hearing in children with CMV-related SNHL. In our cohort, three infants received antiviral treatment—one for early-onset severe unilateral SNHL, one for moderate delayed-onset SNHL, and one for neurological symptoms with MRI abnormalities. All three showed stable hearing thresholds and no neurodevelopmental deterioration over follow-up. However, these are purely descriptive observations, and no inference can be made about treatment efficacy. Given the observational nature of our study, the absence of a control group, and the small number of treated patients, no definitive conclusions can be drawn regarding causality or efficacy. Our results are consistent with previous research suggesting potential benefits of early intervention, but they cannot be generalized beyond the specific context of our cohort. Although current guidelines recommend antiviral therapy only for symptomatic infants with moderate to severe disease, further randomized controlled trials are essential to evaluate whether targeted treatment—particularly in cases with isolated SNHL or predictive markers—may be beneficial. Until such data become available, our findings should be viewed as hypothesis-generating rather than confirmatory. In three cases, although treatment criteria were met, antiviral therapy was refused by the parents after detailed counseling. This underscores the importance of shared decision-making in the management of congenital CMV infection, as previously emphasized in clinical practice guidelines and expert consensus statements [21].

6. Limitations and future directions

This study has several limitations that should be addressed in future research. The small sample size and variability in follow-up duration may have limited the statistical power to detect significant associations in some areas. Additionally, the reliance on clinical data from a single center may limit the generalizability of our findings. Expanding this research to include multicenter cohorts with standardized follow-up protocols could provide more robust data and improve our understanding of the long-term impacts of cCMV infection.

Future research should also focus on developing and validating predictive models that integrate clinical, virological, and imaging data to improve the early identification of infants at risk for adverse outcomes. Advances in genomic and proteomic technologies may also uncover novel biomarkers for prognosis and therapeutic response, paving the way for personalized medicine approaches in the management of cCMV infection.

7. Conclusions

This study reinforces the significant impact of congenital cytomegalovirus (cCMV) infection on neonatal and long-term outcomes, highlighting its role in SNHL, neurodevelopmental delay, and other sequelae, and underscoring the importance of early identification and intervention in cCMV infection. Universal newborn screening for cCMV, as suggested by several recent studies, could significantly improve the detection of asymptomatic cases and facilitate timely interventions. Given the potential for progressive and delayed-onset SNHL, long-term audiological surveillance extending beyond 2 years of age should be considered essential, both in clinical practice and future research. Comprehensive follow-up protocols that include regular audiological, neurological, and imaging assessments remain critical for all infected infants.

The findings also highlight the need for increased awareness and education among healthcare providers and pregnant women about cCMV infection, particularly regarding preventive measures and the importance of early diagnosis. Strengthening public health initiatives aimed at reducing the incidence of maternal CMV infection and improving access to diagnostic and therapeutic resources will be essential in mitigating the burden of this significant public health issue.

In conclusion, this study provides valuable insights into the clinical and prognostic aspects of cCMV infection, emphasizing the need for a multifaceted approach to diagnosis, management, and follow-up. While significant progress has been made in understanding this complex condition, continued research and innovation are essential to improving outcomes for affected infants and their families.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used [ChatGPT, Version 1.2025.009] in order to check English Language and format References as per journal requirements. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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