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Original article

Congenital cytomegalovirus infection: from suspicion to confirmation

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Abstract

Introduction: Congenital cytomegalovirus (CMV) infection is the most common intrauterine infection and the leading cause of sensorineural hearing loss in childhood. Maternal seroconversion during pregnancy carries a 30% to 75% risk of vertical transmission. Serological surveillance is not indicated. In a confirmed infection there is no effective treatment and, in seropositive pregnant women, reactivation and even reinfection by different strains may occur.

Methods: A retrospective observational study (2008-2018) was conducted, analyzing children born in our hospital that maintained follow-up by suspected congenital CMV (cCMV) infection.

Results: We identified 125 cases of children with suspected cCMV infection. In 91 (72.8%) cases, the mothers had positive IgM; in 23 of them a seroconversion was documented and 4 cases corresponded to reactivation. Only 13 of the pregnant women had immunity to CMV, but 3 of the confirmed cases came from this group. Almost 17% of mothers had an unknown serological status and, in these cases, the suspicion was raised by placental changes, identification of abnormalities on the transfontanellar ultrasound, fetal growth restriction or other clinical signs compatible with CMV infection. cCMV infection was confirmed in 12 cases, 4 of them with sensorineural hearing loss and/or psychomotor development delay.

Discussion: Counseling all pregnant women on prevention strategies has proven to be an effective prophylactic measure. Even though universal screening for CMV in pregnant women remains unrecommended, studying children with suspected clinical signs allows early screening for vertical transmission and early detection of possible sequelae.

Keywords

Cytomegalovirus, early diagnosis, pregnancy, prevention, prognosis, treatment.

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Introduction

Human cytomegalovirus (CMV) is a human-specific deoxyribonucleic acid (DNA) virus that belongs to the Herpesviridae family [1]. Transmission can occur through direct or indirect contact with urine, saliva, oropharyngeal and endocervical secretions, sperm, breast milk, tears, blood products or organs [2]. After primary infection, the virus persists in a latent form. Acquired immunity is not completely protective because the infection can reactivate following several stimuli (inflammation, immune impairment, diseases or treatments with immunomodulating agents), but reinfection by different strains of the virus can also occur [3]. CMV infection is normally asymptomatic in immunocompetent individuals, but it can be life-threatening in immunocompromised patients and it is currently the leading cause of congenital viral infection worldwide. Seroprevalence rates vary from 41% to 96.4% in different European countries depending on age, parity, ethnicity, social-economical status, sexual activity and occupation (higher risk in occupations involving close contact with children under 3 years old) [3-6].

Congenital cytomegalovirus infection

Congenital CMV (cCMV) infection has an estimated worldwide incidence of 0.6% to 0.7% of all live births [5, 7]. Prevalence in Portugal is estimated at 0.4% [8]. However, probable CMV seroprevalence in women of childbearing age is nearly half [9]. Intrauterine CMV transmission may occur in women without preexisting immunity who develop a primary infection during pregnancy or in those with preexisting antibodies to CMV by reactivation of the latent virus or infection by a different strain [10]. Although CMV transmission is more likely after primary infection, in populations with high CMV seroprevalence two-thirds of infants with cCMV infection are born to women with preexisting CMV immunity [11].

The rate of vertical transmission increases with gestational age, but there is a higher risk of fetal damage if the infection occurs during the early stages of pregnancy [3, 5]. cCMV infection may result in several clinical scenarios from asymptomatic infection to adverse pregnancy outcomes (stillbirth, neonatal death, intrauterine fetal restriction, preterm birth), maternal pregnancy complications (preeclampsia) or fetal injuries (sensorineural hearing loss, vision loss, optic atrophy, strabismus, chorioretinitis, hepatosplenomegaly, thrombocytopenia, petechiae, jaundice, microcephaly, seizures and mental disability) [1, 5]. After primary maternal infection, symptomatic disease will be present in 10-15% of the infected newborns with cCMV infection [7] and 40% to 58% of them will experience permanent long-term sequelae [12]. Nevertheless, 15% of initially asymptomatic CMV-infected newborns will develop long-term neurological sequelae before the age of 5 years [1].

Maternal cytomegalovirus infection identification

The majority of maternal CMV infection during pregnancy is not recognized. Only 10% of the women who became seropositive report a febrile illness and rarely a mononucleosis-like infection [4]. The diagnosis of maternal CMV infection is based on the IgG antibody detection in a previously known nonimmune pregnant woman. In order to detect a primary infection, serological testing for CMV should be available in the early stages of the pregnancy [13]. However, since serologic CMV screening is not routinely performed, that information is not always available [12]. The conversion of a negative to positive IgM or a 4-fold increase in IgG antibody titer over a 4 to 6 week period, combined with an avidity test of CMV IgG, allows the diagnosis of a recent infection. Low avidity indicates an infection that occurred in the previous 3 to 4 months and implies an increased risk of fetal/newborn transmission. High avidity during the 1st trimester excludes postconception primary infection, suggesting a low risk of intrauterine transmission. An intermediate avidity result in the 1st trimester indicates a low risk of fetal transmission, but if it occurs later it does not rule out a postconception primary

infection and implies an increased risk of vertical transmission [14]. Universal screening for CMV in pregnant women is not cost-effective and is not recommended because: there is no effective vaccine or therapy to prevent fetal transmission nor to treat cCMV; infection can occur after seroconversion, reinfection or reactivation in seropositive women; most children with cCMV infection are asymptomatic and even fewer develop late-onset sequelae.

Fetal cytomegalovirus infection detection

Fetal infection can be determined through an amniocentesis followed by a CMV DNA Polymerase Chain Reaction (PCR) analysis or virus culture. These tests are considered gold-standard with a 75-100% sensitivity and a 67-100% specificity [4]. Amniocentesis should be performed at least 6 weeks after primary maternal CMV infection to achieve detectable viral loads in the amniotic fluid, and after 21 weeks of gestational age because CMV is excreted into the amniotic fluid through fetal urine and fetal urination is established around the 21st week of gestation. However, we should keep in mind that amniocentesis is an invasive procedure with both maternal and fetal risks and a negative result does not rule out fetal infection [4, 15] and, for that reason, the decision should be tailored to each case. Cordocentesis has also been appointed as an alternative method to quantify fetal CMV and measure antibody response to infection. It may contribute with valuable information about the clinical outcome of a cCMV infection as high viral load in fetal blood has been associated with symptomatic infected fetuses [4]. However, similar to amniocentesis, it implies a high risk of complications such as spontaneous abortion [4]. PCR assays for CMV DNA in maternal urine or serum and CMV DNA in uterine cervical secretions have also been studied as potential methods to predict cCMV infection amongst CMV seropositive pregnant women, but neither of them has proven to be useful [15]. For fetuses with positive isolation of the virus, termination of the pregnancy can be offered as an option. If the decision is to continue with the pregnancy, close follow-up with regular ultrasound exams is essential.

Ultrasound fetal abnormalities usually associated with cCMV infection are cerebral ventriculomegaly, microcephaly, lenticulostriate vasculopathy, hyperechogenic fetal bowel, hepatosplenomegaly, cerebral periventricular echogenicity/intracranial calcifications, fetal growth restriction, abnormal amniotic fluid volume, placental enlargement, ascites and fetal hydrops [4, 10]. Magnetic resonance imaging is described as a more sensitive test to detect fetal intracranial abnormalities, but analysis of the results can be challenging [15]. Additional research is needed to distinguish fetuses with cCMV infection that will or will not develop significant Central Nervous System (CNS) damage.

Administration of CMV hyperimmune globulin to pregnant women with primary CMV infection has been evaluated for prevention of vertical transmission and a study has described high-dosage valacyclovir as being effective in improving the outcome of infected fetuses [16]. Nevertheless, results have been inconsistent and antivirals should not be routinely administered [4].

A vaccine against cCMV infection could potentially have economic benefits, there are some reports demonstrating their immunogenicity and hypothetical efficacy, but to date no vaccine has been licensed [17].

Diagnosis, treatment and prevention of congenital cytomegalovirus infection

Strategies to reduce the burden of cCMV-associated sequelae involve neonatal screening for early detection and intervention and, in some cases, neonatal antiviral therapy [5]. Most infected infants are asymptomatic at birth so, unless some event during pregnancy raises suspicion, a large number of newborns with cCMV infection will develop hearing loss or neuromotor disabilities during the first years of life. Universal hearing screening at birth with otoacoustic emission detects symptomatic hearing impairment at birth [2], but more than two-thirds of patients with cCMV infection will only develop hearing loss months to years after birth [2, 18] and will not be detected with this screening test.

Virus isolation in tissue culture from urine samples or PCR testing for CMV within the first 2 weeks of life are considered gold-standard for cCMV infection diagnosis [2, 19]. These methods are not convenient for universal screening because they are labor- and resource-demanding. There are some alternative methods such as real-time PCR assays in dried blood spots, but this test is also not suited for mass screening [19]. There have been some reports demonstrating the utility of saliva

PCR assay to screen newborns and the results are promising with high sensitivity (100%; 95% CI, 95.8-100%) and specificity (99.9%; 95% CI, 99.8-99.8%) [20, 21].

Studies on the use of antivirals have shown that ganciclovir can preserve normal hearing or prevent hearing loss progression as well as improving long-term neurodevelopmental outcomes when initiated within the first 4 weeks of life and taken during a period of 6 weeks to 6 months [22]. Valganciclovir, an oral prodrug of ganciclovir, is the first-line treatment option unless there is severe symptomatic CNS disease or the infant is unable to tolerate oral medication [23]. Symptomatic neonates with significant disease at birth, including multi-system organ failure, growth retardation, neurodevelopmental problems and sensorineural hearing loss, are considered candidates for pharmacological treatment. Infants with asymptomatic infection or CMV-related morbidity that develops beyond the neonatal period should not receive antiviral therapy and should be prospectively monitored for late-onset hearing loss and developmental delays [5, 24]. Early intervention is crucial in minimizing the impact of hearing loss on language development and other development domains, as well as decreasing the burden of global developmental delays in infected children and their future lives.

Methods

The authors performed a retrospective observational study on children with suspected cCMV infection at birth. Data were collected from the clinical files of patients born in Centro Hospitalar Entre-o-Douro-e-Vouga, Hospital de São Sebastião (CHEDV-HSS), between 2008 and 2018 with suspected cCMV infection.

The main reasons for suspicion were: altered maternal CMV serologic tests during pregnancy, abnormal prenatal ultrasound, postnatal cerebral ultrasound alterations, fetal growth restriction and thrombocytopenia. The diagnosis of cCMV infection was made by a positive shell vial assay or positive PCR-CMV urine test within the first 2 weeks of life, or a PCR-CMV test confirmed on Guthrie card for older infants.

A descriptive statistical analysis of the demographic, serological and clinical data was performed using Microsoft® Excel® and IBM® SPSS® statistical package, version 23. Continuous variables were analyzed and results were expressed as the mean ± standard deviation and were compared using Student's t-test. Qualitative variables were described as numbers and percentages and frequencies were compared using Fisher's exact test or the Chi-square test. A p-value ≤ 0.05 was considered statistically significant.

Results

From 2008 to 2018, there were 21,049 live births registered at CHEDV-HSS. The authors identified 125 cases of suspected cCMV infection. Of these, 12 cases were confirmed, with an infection rate of 0.06%.

The median maternal age was 30.8 years (minimum 15, maximum 45 years). Sixty-nine (55.2%) women were having their 1st child, 46 (36.8%) their 2nd child, 8 (6.4%) their 3rd child and 2 (1.6%) their 4th child. Ninety-six percent of women had normal pregnancy surveillance and 70% had no complications throughout the pregnancy. Among those who had complications, gestational diabetes was the most frequent (n = 16), followed by oligoamnios/polyhydramnios (n = 7), gestational hypertension (n = 3), intrahepatic cholestasis of pregnancy (n = 2), anemia (n = 1), thrombocytopenia (n = 1), risk of preterm birth (n = 1) and premature rupture of membranes (n = 1). We found only 2 cases with placental changes compatible with a Toxoplasmosis, Others (Syphilis, Varicella-Zoster, Parvovirus B19), Rubella, CMV and Herpes infection (TORCH infection).

In **Tab. 1**, the characterization of the study population by maternal serological status is presented, as well as the distribution of the confirmed cases between these groups.

Maternal primary CMV infection, in which seroconversion from IgM negative to IgM positive was documented, occurred in 23 (18.4%) pregnancies. Within these, 8 (34.8%) were documented in the 1st trimester, 9 (39.1%) in the 2nd trimester and 6 (26%) in the 3rd trimester. Five (41.7%) of the proven cCMV cases came from this group of mothers. Out of all the 125 pregnant women, in 48 cases (38.4%) the maternal serological status was not informative of the timing of the possible infection: 39 (81.3%) had a positive IgM antibody with a positive IgG antibody with a high avidity test in the 2nd or 3rd trimester, 5 (10.4%) had a positive IgM antibody with a positive IgG antibody with a low or unknown avidity test, 1 (2.1%) had a negative IgM antibody with a positive IgG antibody in the 3rd trimester

Table 1. Characterization of study population by maternal serological status.

	Seroconversion	Reactivation/ reinfection	Past infection with IgM-, IgG+	Recent infection with IgM+, IgG+/IgG-	Unknown
Mothers	23	4	13	64	21
Maternal age	31.8	30.8	31.8	29.8	30.5
First child	43.5%	50%	53.8%	50%	85.7%
Gestational age	38.9	38.8	38.1	38.7	38.3
Confirmed cases	5	0	3	3	1
Symptoms	1	-	2	0	1
Outcome	1 psychomotor development delay	-	1 death, 1 psychomotor development delay with hearing loss	1 hearing loss	1 hearing loss

and 3 (6.3%) had a positive IgM antibody with a negative IgG antibody (one in each trimester). Reactivation or reinfection was identified in only 4 (3.2%) of the pregnant women, by an increasing title of IgG antibody or positivation of previously negative IgM with a persistent positive IgG, but there were no confirmed cases in this group. In 21 (16.8%) of the suspected infants, maternal serological status for CMV infection was still unknown at the time of the birth and the suspicion was raised due to changes in transfontanellar ultrasound in 15 cases, clinical findings in 5 patients (hearing loss, small for gestational age, hepatosplenomegaly, petechiae, neonatal seizures, intestinal microcalcifications), and 1 patient had a documented choroid plexus cyst in a prenatal ultrasound. One of these newborns was a proven case of cCMV infection, with a severe clinical manifestation and a poor outcome.

A total of 22 (17.6%) pregnant women were submitted to amniocentesis and in 16 cases (72.7%) the maternal serological profile was compatible with possible CMV infection during the 1st trimester. All results of PCR analysis of the amniotic fluid for CMV DNA were negative.

Case analysis revealed a mean gestational age of 38.6 weeks (minimum 28 weeks, maximum 41 weeks) with 8.8% prematurity. There were 59 (47.2%) male and 66 (52.8%) female suspected cases, with an average birth weight of 3,094 g (minimum 1,030 g, maximum 4,500 g).

Only 11 of the infants (8.8%) presented with symptoms in the neonatal period (hypoglycemia, thrombocytopenia, anemia, hepatosplenomegaly, disseminated intravascular coagulation, hypertonia/hypotonia, cholestatic jaundice). In 19 cases (15.2%), transfontanellar ultrasound changes were described (lenticular-striated vasculopathy, thalamic calcifications, intraventricular hemorrhage, base nuclei calcifications, subependymal hemorrhage) and this was the only detail that raised suspicion of a cCMV infection. In total, there were 39 newborns with altered transfontanellar ultrasound, but only 4 were confirmed to have cCMV infection. Of these, 1 died and 2 developed sensorineural hearing loss and development disabilities.

The confirmed cases are described in **Tab. 2**. Seven cases (58.3%) were diagnosed by identification of a positive PCR-CMV in the newborns' urine, 2 from a positive PCR-CMV in the blood, 2 from a positive PCR-CMV result in the Guthrie card and 1 diagnosis was made post-mortem. Five (41.7%) of the confirmed cCMV infected cases were born to mothers with a documented seroconversion during pregnancy. Four (33.3%) of the infected newborns were symptomatic at birth; 1 of them died and 2 of them developed long-term sequelae. The median maternal age was 30.8 years (minimum 20 years, maximum 39 years) and median maternal age for confirmed cases was 31.7, but this difference was not statistically significant. There was an average of 37.4 weeks of gestational age, with 16.7% of prematurity and no statistical difference was found between them. The mean birth weight was 3,000 g, but in confirmed cases the mean birth weight was 2,700 g, and the difference was statistically significant ($p = 0.014$). In the group of children with cCMV infection, 58.3% of mothers had a previous child compared to 44.3% of women with suspected but not confirmed infected infants, a difference that was not statistically significant.

Discussion

A Swedish group showed an estimated prevalence of 0.2% for cCMV infection based

Table 2. Description of confirmed cases with congenital cytomegalovirus (CMV) infection.

Case no. and gender	Maternal serological status	Prenatal ultrasound	Amniocentesis	Gestational age	Birth weight	Neonatal signs and symptoms	Ultrasound changes/ Neonatal auditory screening/ Visual screening	Follow-up/ Psychomotor development
Case 1, M	IgM+, IgG+ (3rd trimester with high avidity)	Normal	No	39	AGA	No	Thalamic vasculopathy/ Normal/Normal	Sensorineural hearing loss
Case 2, M	Seropositivity	Fetal hydrops	No	29	AGA	Severe perinatal asphyxia, disseminated intravascular coagulation, death	Intraventricular hemorrhage grade IV/- /-	Absent [a]
Case 3, F	Seropositivity	Fetal growth restriction, oligoamnios	No	37	Light for GA	Thrombocytopenia, cutaneous hemorrhage	Base nuclei calcifications/ Normal/Normal	Psychomotor development delay, sensorineural hearing loss
Case 4, M	Unknown	Fetal growth restriction, hydramnios, suspected esophageal atresia	No	38	Light for GA	Sepsis, thrombocytopenia, cholestatic jaundice, hepatosplenomegaly, purpuric nodules (treated with ganciclovir)	Normal/ Normal/-	Sensorineural hearing loss
Case 5, M	Seropositivity	Normal	No	39	Large for GA	No	Thalamic calcification, lenticular-striated vasculopathy/ Normal/-	Adequate
Case 6, M	Seroconversion (3rd trimester)	Normal	No	39	AGA	No	Normal/ Normal/Normal	Adequate
Case 7, M	Seroconversion (1st trimester)	Normal	Yes (PCR negative)	39	AGA	No	Normal/ Normal/-	Adequate
Case 8, F	Seroconversion (1st trimester)	Normal	Yes (PCR negative)	36	AGA	Thrombocytopenia	-/Normal/ Normal placenta with signs of TORCH infection	Adequate
Case 9, F	Seroconversion (3rd trimester)	Normal	No	38	AGA	No	Normal/ Normal/Normal	Psychomotor development delay
Case 10, F	IgM+, IgG+ (2nd trimester with high avidity)	Fetal growth restriction	No	38	AGA	No	-/Altered/ Normal	Adequate
Case 11, F	IgM+ (pre-conceptional; 1st trimester with low avidity)	Normal	No	39	AGA	No	Normal/ Normal/-	Adequate
Case 12, F	Seroconversion (2nd trimester)	Normal	No	39	AGA	No	Normal/ Normal/-	Adequate

AGA: appropriate for gestational age; GA: gestational age; PCR: Polymerase Chain Reaction.
[a] Death.

on universal screening using real-time PCR to identify CMV DNA in dried blood spots [25]. A Portuguese study found a similar prevalence of 0.4% by using urine samples. Our study estimates an incidence of 0.06% in our population in a 10 year period, based on high criteria for suspected cCMV infection, either by maternal serological profile or clinical manifestations and imaging features suggestive of cCMV infection. There may be an underestimation of the diagnosis because

most of the affected infants are asymptomatic at birth and most pregnant women have an unknown CMV serological state.

There is a 30% to 40% risk of vertical transmission when primary maternal infection occurs, especially in the 1st trimester [26]. In our study, 23 (18.4%) pregnant women had a proven seroconversion, 8 of them in the 1st trimester. In 5 of these, cCMV infection was confirmed.

The rate of cCMV infection in the population of CMV-immune women at the time of conception (non-primary maternal infection) ranges from 0.1% to 1%, depending on the overall prevalence of CMV infection [4]. In our study, we identified 3 cases (11.5%) of cCMV born to the 26 mothers who were immune to CMV or had a high IgG avidity that excluded postconception primary infection. In these cases, the suspicion was based on suggestive clinical manifestations in fetuses or newborns (1 hydrops fetalis, 1 fetal growth restriction and 1 with thalamic calcifications).

Approximately 50% of newborns with cCMV infection who have signs or symptoms of intrauterine infection at birth will develop long-term disabilities. Approximately 5% to 15% of initially asymptomatic CMV-infected newborns will also develop long-term neurological sequelae before the age of 5 years old [1]. Most of the infected children in our series (8 out of 12) were asymptomatic at birth and in 16.8% of the cases, suspicion was only raised in the postnatal period, and so a high level of suspicion is required.

Various authors sustain that when maternal infection takes place in the 3rd trimester the rate of vertical transmission is around 75%, but the disease is mostly asymptomatic. In 2 cases of seroconversion in the 3rd trimester, 1 was asymptomatic and the other developed neurodevelopment impairment.

We found that confirmed cases of cCMV infection were born with significantly lower birth weight, so fetal growth restriction and small for gestational age may be useful predictors of cCMV infection.

Contact with saliva and urine of children with cCMV infection is one of the most common ways to be exposed to CMV, so pregnant women with a previous child are at higher risk of primary maternal infection [27]. In our study, 56 (44.8%) women had more than 1 child and only 13 (23.2%) of these women had seroconversion to CMV during pregnancy. No statistical difference was found between infected and suspected newborns as to the existence of siblings.

Conclusion

Maternal CMV infections during pregnancy are usually not clinically recognized and universal maternal screening for CMV infection is not recommended. Preconceptional screening for CMV could permit a correct interpretation of serological and virological tests in case of a primary infection. Appropriate counseling providing educational guidance to limit exposure to CMV has proven to lower CMV seroconversion rate during pregnancy. The target population should include both CMV-seronegative and CMV-seropositive women prone to reinfection. Hygienic intervention strategies include washing hands whenever there is contact with a child's saliva or urine, avoiding kissing children or sharing food, drinks and other utensils that might have been exposed to children's biological fluids [5].

The use of antivirals, specific immunoglobulin or a vaccine is not currently recommended. The most effective way to prevent maternal infection is based on preventive measures. Advising all pregnant women, providing information on sources of CMV and hygiene education has proven to reduce the infection rate.

Due to the importance of early diagnosis of hearing loss or development delay, irrespectively of the maternal serological profile, the implementation of universal screening of all newborns would probably be beneficial.

Declaration of interest

The Authors declare that there is no conflict of interest.

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