CASE REPORT

Cytomegalovirus Congenital Infection. Do We Know What We Do Not Know?

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Abstract

Congenital cytomegalovirus infection is the most frequent vertical infection in developed countries and one of the main causes of sensorineural hearing loss and neurodevelopment delay. Despite its high incidence, this infection remains underdiagnosed, with untreated cases and significant risk of sequelae. In this area, randomized clinical trials are scarce, and therapeutic guidelines with ganciclovir or valganciclovir are based on expert consensus. Current knowledge about the high genetic variability of cytomegalovirus, on the other hand, makes it difficult to establish preventive measures and strategies to approach neonatal infection. From three clinical cases of variable severity, the authors discuss dilemmas and challenges of congenital cytomegalovirus infection.

Keywords: Cytomegalovirus Infections/complications; Cytomegalovirus Infections/therapy; Cytomegalovirus Infections/transmission; Infant, Newborn; Infectious Disease Transmission, Vertical; Pregnancy Complications

Introduction

Cytomegalovirus (CMV), from the *Herpesviridae* family, is a virus of global distribution, infecting all age ranges and socioeconomic groups.[1] It is the most frequent congenital infection in developed countries, affecting 0.3%-2.4% of all newborns.[1] It is the most frequent cause of non-hereditary sensorineural hearing loss, and the second cause of neurodevelopment delay.[2] Its epidemiology and natural history are still poorly understood. In the neonatal period, 90% of the infected patients are asymptomatic, of which 10%-15% develop long-term sequelae.[3] In Portugal, prevalence is estimated at 0.7%-1%.[4] However, several studies suggest that congenital CMV remains underdiagnosed, propitiating untreated cases with risk of sequelae.[1] Furthermore, randomized clinical trials in this area are scarce, and guidelines are based on expert opinion consensus. Therefore, the absence of robust international recommendations regarding prevention, diagnosis, or therapy, together with the vast genetic variability of the virus,[5] hamper the establishment of systematic approach strategies. The authors present three cases of congenital CMV infection of variable severity and discuss difficulties in the complex decision-making process.

Case Report

Case Report 1

A 30-year-old pregnant woman, with negative serologies for CMV in the beginning of pregnancy. In the second trimester, without maternal symptoms, seroconversion was detected with positive immunoglobulin (Ig) M and IgG and low IgG avidity. Amniocentesis was performed, and positive CMV polymerase chain reaction (PCR) in the amniotic fluid confirmed fetal infection. Fetal magnetic resonance imaging (MRI) revealed ventriculomegaly, cerebral calcifications, and periventricular hyperechogenicity. Parents refused pregnancy interruption and specific immunoglobulin was offered to the mother, who also did not accept. A female child was delivered at 39 weeks of gestational age, with a birth weight of 2930 g, in the 25th percentile (P), and 32.5 cm of head circumference (P12). Cranial ultrasonography performed on the first day of life revealed ventriculomegaly, bilateral subependymal cysts, scattered calcifications in the cerebral, periventricular, basal ganglia and cerebellum parenchyma and bilateral thalamostriate vasculopathy. In the sixth day of life, serum viral load for CMV was 4,798 copies/mL and thrombocytopenia and unconjugated hyperbilirubinemia were detected. In the 10th day of life, hearing assessment revealed sensorineural hearing

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loss with moderate involvement on the left (50%) and severe on the right (85%). Valganciclovir was started from the first week of life, without any associated adverse effects. The blood viral load was negative one month after starting treatment. She is currently 2 years and 10 months old, presenting deep right hearing loss (100%), but with normal hearing on the left, normal ophthalmological evaluation and neurodevelopment.

Case Report 2

A 32-year-old pregnant woman, without preconceptional screening for CMV, presenting severe intrauterine growth restriction with no identified cause. A female child was delivered at 40 weeks of gestational age with birth weight of 1,765 g (< P1) and 32 cm of head circumference (P25). She presented with thrombocytopenia and neonatal hepatitis, with slow but progressive normalization of liver enzymes. Cranial ultrasonography showed periventricular hyperechogenicity and bilateral thalamus vasculopathy. In the seventh day of life negative IgM and positive IgG for CMV were detected with serum viral load of 1,830 copies/mL and associated 42,830,060 copies/mL in the urine. Simultaneously, the mother presented positive IgM and IgG with low IgG avidity, suggesting gestational infection in the third trimester. Hearing and ophthalmologic evaluation were unremarkable. Valganciclovir was started in the 21st day of life, with viral load negativization in two months without any reported adverse effects. Cranial ultrasonography and brain MRI performed at 5 and 12 months, respectively, were normal. Currently, she is 22 months old, exhibiting normal vision and hearing, but displaying mild neurodevelopment delay (areas of manipulation, speech and language corresponding to 15 months on the Schedule of Growing Skills-II (SGS-II) scale, with other areas corresponding to 18 months).

Case Report 3

A 28-year-old pregnant woman, with negative preconceptional serologies for CMV. In the second trimester, after a flu-like syndrome, CMV maternal primoinfection was confirmed with positive IgM and IgG and low IgG avidity. Amniocentesis confirmed fetal infection with the detection of 3,400 copies/mL in the amniotic fluid. Fetal MRI was normal. A female child was delivered at 39 weeks of gestational age with birth weight of 2,865 g (P25) and 33 cm of head circumference (P25). Cranial ultrasonography performed in the first day of life revealed bilateral thalamostriate vasculopathy and rare calcifications. On the third day of life serum CMV viral load was 8,000 copies/mL. She remained asymptomatic during the neonatal period and hearing and ophthalmological evaluation were normal. Valganciclovir was started in the fifth day of life, without any reported adverse effects. Blood viral load was negative after three months. In the second month of life, mild bilateral sensorineural hearing loss (20%) was detected and brain MRI revealed hypersignal changes in the cerebellar hemispheres. At 20 months of age, the degree of hearing loss remains stable, requiring no hearing aid. Ophthalmologic evaluation and neurodevelopment, namely the area of language, remains normal to date and the child is currently awaiting MRI revaluation.

Table 1 shows the main differences between the three cases.

Summarizing, diagnosis was confirmed in all patients by the presence of CMV deoxyribonucleic acid (DNA) in the amniotic fluid and/or blood and urine in the first week of life. All newborns were treated with valganciclovir at the dose of 16 mg/kg twice daily for six months. Analytical surveillance of adverse drug reactions was performed at six and eight weeks of treatment, and thereafter monthly until the end of treatment. CMV serum VL was monitored monthly until its negativization. In all cases, cranial ultrasonography, magnetic resonance imaging and ophthalmology / otorhinolaryngology evaluation were performed. All patients are currently in subspecialty outpatient surveillance, with regular hearing and neurodevelopment assessments. Screening and confirmation of neurodevelopment delay was performed using the SGS-II.

Discussion

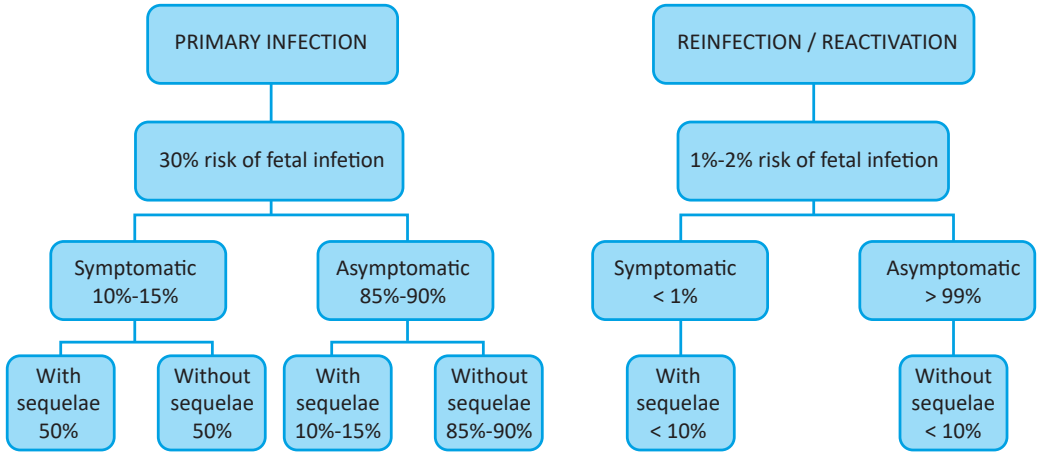
Congenital CMV infection occurs mostly after maternal primoinfection during pregnancy, which occurs in about 1%-4% of seronegative women.[6] Seropositive women may also generate infected fetuses in case of reactivation of an old infection and/or reinfection by different viral strains, although the risk of congenital infection and sequelae is lower (Fig. 1).[1,6] The risk of transmission is directly related to the amniotic fluid viral load and gestational age, being higher at the end of the pregnancy, contrasting with severity, which is superior the earlier the infection occurs.[7]

Sensorineural hearing loss, the main long-term complication of this congenital infection, occurs in 12.6% of all cases (18% of the symptomatic cases and 9% of the asymptomatic infants).[7] It is estimated that one in each five cases of pediatric sensorineural hearing

Table 1. Summary of the presented clinical cases

	Case 1	Case 2	Case 3
Time of infection	Second trimester	Third trimester	Second trimester
Prenatal approach	Positive IgM e IgG, low IgG avidity Positive CMV PCR in the amniotic fluid Fetal MRI: ventriculomegaly, calcifications, periventricular echogenicity	No prenatal diagnosis	Positive IgM e IgG, low IgG avidity Positive CMV PCR in the amniotic fluid (5,400 copies/mL) Normal fetal MRI
Clinical presentation	Bilateral hearing loss, thrombocytopenia, jaundice, ventriculomegaly, subependymal cysts, calcifications, thalamostriate vasculopathy	Severe intrauterine growth retardation, hepatitis, thrombocytopenia, thalamic vasculopathy	Mild thalamostriate vasculopathy, rare calcifications
Serum viral load	8th day of life 4,798 copies/mL	7th day of life 1,830 copies/mL	5th day of life 8,000 copies/mL
Breast milk	No	No	No
Follow up	2 years and 8 months Normal neurodevelopment Right hearing loss (100%), normal left hearing Normal ophthalmologic evaluation	20 months Mild neurodevelopment delay Normal ophthalmologic and audiological evaluation	18 months Normal neurodevelopment Bilateral hearing loss (20%) Normal ophthalmologic evaluation

CMV - cytomegalovirus; Ig - immunoglobulin; MRI - magnetic resonance imaging; PCR - polymerase chain reaction.



Adapted from: Britt W. Cytomegalovirus. In: Wilson C, Nizet V, Maldonado Y, Remington J, Klein J, editors. Infectious diseases of the fetus and newborn infant. 7th ed. Philadelphia: Elsevier; 2011.p.706-55.[25]

Figure 1. Scheme of the risk of fetal viral transmission, symptoms, and sequelae according to the type of infection.

loss is due to congenital CMV infection.[7] Prognosis improves the earlier the infection is detected and the intervention is started, thereby making it potentially preventable or treatable.

In Portugal, the Directorate-General of Health (DGS) advises the preconceptional screening of CMV specific antibodies, which, in case of clinical or ultrasonographic suspicion of primoinfection, will enable the comparing of laboratory values and facilitate diagnostic procedures.[8] Despite all this, universal CMV screening in pregnancy is not recommended. Some of the reasons include the prognostic unpredictability of infected fetuses and the absence of effective fetal transmission preventive measures.[9] Therefore, asymptomatic cases, not identified at birth, may be diagnosed too late to initiate antiviral therapy, which, in the light of current evidence, has a beneficial effect on hearing and neurodevelopment, if initiated in the first month of life.[10,11] Regarding pregnancy infection, parents and clinician knowledge is limited, and there is no routine discussion with women prior to the conception.

Diagnosis of congenital CMV infection is performed by identifying viral genome in the urine, blood, saliva, or cerebrospinal fluid in the first three weeks of life in order to exclude transmission acquired during delivery or through breastfeeding. Of all the seropositive mothers, 66%-96% excrete CMV in their breast milk,[12] which may hamper the distinction between congenital and acquired infection. CMV PCR in the newborn saliva, performed up to two hours of life, due to its easy execution and high

sensitivity, is a promising method and can become a gold-standard test. In late clinical suspicion, it is possible to retrospectively diagnose congenital infection using the polymerase chain reaction of the Guthrie cards of the neonatal screening, with a sensitivity ranging between 71% and 100%.[13] Due to the high prevalence of this infection and since there is evidence of a cost-effective program with an impact in the prevention and treatment of sensorineural hearing loss,[14] universal neonatal screening is a possible reality in the future.

Clinical, laboratory, and imaging manifestations of the newborn, summarized in Table 2, may suggest the diagnosis, as happened in the second case, which had no prenatal diagnosis. In 8% of the symptomatic cases, there are severe manifestations with a reported mortality of 10%-30%.[13] Severity grading is fundamental, since it implies different degrees of approach and treatment.[3,14,15] In 85%-90% of the cases, infection is asymptomatic, and laboratory and imaging findings are fundamental to define the approach.[15] Severity grading includes[3,16,17]:

1. Severe disease: Systemic or organ life-threatening manifestations and/or central nervous system involvement;
2. Moderate disease: More than two non-life-threatening manifestations and/or manifestations that persist for more than two weeks;
3. Mild disease: Up to two mild or transient manifestations;
4. Asymptomatic or isolated hearing loss.

Expert recommendations for antiviral therapy are based on two randomized clinical trials with six weeks of ganciclovir,[10,18] and in one randomized clinical trial with six months of valganciclovir.[11] The latter, not currently approved by the Portuguese regulatory authorities (Infarmed) for congenital CMV infection, has been progressively used as an off-label option in Europe and in the US. Table 3 summarizes the recommendations for antiviral therapy, based on working groups and expert recommendations. Due to the lack of a significant number of randomized clinical trials, the literature is unclear whether mild cases, asymptomatic, and with isolated hearing loss should receive antiviral therapy.

The first case represents a severe infection, which even motivated a proposal for pregnancy termination. Indication for antiviral therapy was unquestionable, and a good clinical evolution was observed. In the second case, of moderate severity, with intrauterine growth restriction hepatitis and thrombocytopenia, the decision to initiate antiviral therapy was individualized. Thus, in view of the neuroimaging findings, not pathognomonic, but frequently observed in this condition, valganciclovir was started. The current neurodevelopment delay at 22 months leaves open the possibility of a worse prognosis in the absence of treatment. The third case, clinically asymptomatic and with no hearing loss, presented discrete alterations in the cranial ultrasonography whereby the indication to treat was debatable. The

Table 2. Clinical, laboratory, and imaging findings in congenital cytomegalovirus infection

Clinical manifestations
• Intrauterine growth restriction, microcephaly
• Petechiae, purpura, blueberry muffin rash
• Prolonged jaundice
• Hepatosplenomegaly
• Pneumonitis with respiratory insufficiency
• Lethargy, hypotonia, seizures, feeding disorder
• Sensorineural hearing loss
• Chorioretinitis
Laboratory results
• Thrombocytopenia
• Hemolytic anemia
• Leukopenia, neutropenia
• Elevated liver enzymes
• Conjugated hyperbilirubinemia
• Cerebrospinal fluid pleocytosis
Neuroimaging
• Periventricular calcifications or ventriculomegaly (suggestive)
• Lenticulostriate vasculopathy, periventricular cysts, periventricular leukomalacia cortical atrophy cerebellar hypoplasia

Adapted from (with authorization): Luck SE, Wieringa JW, Blázquez-Gamero D, Henneke P, Schuster K, Butler K, et al. Congenital cytomegalovirus: A european expert consensus statement on diagnosis and management. Pediatr Infect Dis J 2017;36:1205-13.

Table 3. Antiviral therapy recommendations for congenital cytomegalovirus infections[3,16,17]

Clinical or imaging involvement of the central nervous system	Initiate treatment (A1)
Severe organ disease or life-threatening manifestations	Initiate treatment (B1)
Moderate disease	Consider treatment (C1)
Isolated sensorineural hearing loss	Consider treatment (C2)
Mild disease	No treatment (C2)
Asymptomatic	No treatment (D2)

GRADE system of evaluating evidence:

A - High: Further research is very unlikely to change our confidence in the estimate of effect. Based on randomized trials or double-upgraded observational studies.

B - Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Based on downgraded randomized trials or upgraded observational studies.

C - Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Based in double-downgraded randomized trials or observational studies.

D - Very Low: Any estimate of effect is very uncertain. Based in triple-downgraded randomized trials, or downgraded observational studies, or case series/case reports.

Strength of recommendation:

1 - Strong: Most informed patients would choose the recommended management and clinicians can structure their interactions with patients accordingly.

2 - Weak: Patients' choices will vary according to their values and preferences, and clinicians must ensure that patient care is in keeping with their values and preferences.

discussion of risks and benefits with the infant legal representatives led to the decision to carry out the treatment. Nevertheless, bilateral sensorineural hearing loss and neuroimaging changes were observed, despite normal neurodevelopment. This case opens the discussion for the unpredictability and great individual variability of CMV infection. Clinical severity, treatment efficacy and risk of sequelae may be associated with the vast genetic variation wild strains exhibit.[5,19] In recent years, effort has been made to relate different strains to the clinical severity and risk of sequelae. Capsule glycoproteins, such as UL55, UL144, US28, and UL146, were postulated as markers of pathogenicity and virulence.[19,20] Some authors reported an association between UL144 A and C genotypes and symptomatic congenital disease. On the other hand, genotype B infected fetuses had a lower viral load and better prognosis,[19,20] although these findings were not always consistent in other series.[19,21,22] In addition, genetic and immune host susceptibility, either by maternal[23] or fetal polymorphisms,[24] may play an important role in the risk of fetal transmission. Although promising, the relationship between clinical indicators and virulence factors is not scientifically reproducible to date. Therefore, it is difficult to state that, even in asymptomatic children, there is no indication for antiviral association. Lack of knowledge about this infection is potentially greater than the knowledge we currently dispose. Only further investigation into the role of certain viral genotypes and individual polymorphisms as prognostic markers may influence decision making.

WHAT THIS CASE REPORT ADDS

- These cases reflect the great variability of congenital cytomegalovirus infection, making the results difficult to predict at the individual level.
- Issues such as the legitimacy of performing treatment in mild or asymptomatic cases or in children older than 12 months, will remain controversial. A better understanding of the viral genome and the advent of new genotyping techniques may enable the individualization of a clinical and prognostic profile.
- Lack of knowledge in the community about this type of infection, coupled with the absence of routine testing, screening, or vaccination programs, perpetuate this problem, which is surely underestimated.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

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Infeção Congénita Por Citomegalovirus. Sabemos o Que Não Sabemos?

Resumo:
A infeção congénita por citomegalovírus é a infeção vertical mais frequente em países desenvolvidos e uma das principais causas de surdez neurosensorial e atraso psicomotor. Apesar da sua elevada incidência, esta infeção permanece subdiagnosticada, com casos não tratados e risco importante de sequelas. Nesta área, os ensaios clínicos aleatorizados são escassos e as orientações terapêuticas com ganciclovir ou valganciclovir são baseadas em consensos de peritos. O atual conhecimento sobre a elevada variabilidade genética do citomegalovírus, vem por outro lado dificultar a instituição de medidas preventivas e estratégias de abordagem da infeção neonatal. A partir de três casos clínicos de gravidade variável, os autores discutem dilemas e desafios da infeção congénita por citomegalovírus.

Palavra-Chaves: Complicações na Gravidez; Infecções por Citomegalovirus/complicações; Infecções por Citomegalovirus/tratamento; Infecções por Citomegalovirus/transmissão; Recém-Nascido;Trasmissão Vertical de Doença Infeciosa