Congenital cytomegalovirus infection: clinical findings and outcome in patients from a tertiary paediatric hospital in Florianópolis

Infecção congênita pelo citomegalovírus: achados clínicos e desfecho em pacientes de um hospital pediátrico terciário de Florianópolis

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ABSTRACT

Introduction: Cytomegalovirus (CMV) is a widely disseminated virus, capable of remaining latent and reactivating, with high global seroprevalence. In Brazil, seroprevalence exceeds 95%, with primary infections predominating in childhood. **Objective:** To describe the clinical profile at birth and outcome at 12 months of age of patients diagnosed with congenital cytomegalovirus infection in a reference pediatric hospital in Florianópolis from 2017 to 2022. **Methods:** This was a retrospective, observational and descriptive study with secondary data analysis. The research was approved by the Human Research Ethics Committee. **Results:** Of the 20 cases included in the study, 12 (60%) were female and all were white coloured. 14/17 (82.3%) of the cases were full-term births and 14/16 (87.5%) had a low birth weight for gestational age. Jaundice was identified in 7/13 (53.8%), microcephaly in 5/18 (27.7%), conjugated hyperbilirubinemia in 5/8 (62.5%) and intracranial calcifications in 9/20 (45%) records. 6/20 (30%) cases failed the neonatal hearing screening and 5/20 (25%) presented bilateral loss of brainstem auditory evoked potential. At 12 months of age, bilateral hearing loss and microcephaly were found in 5/8 (62.5%) and 7/13 (53.8%) cases respectively. **Conclusion:** Low birth weight for gestational age, jaundice and microcephaly were prevalent changes. Intracranial calcifications were the most common neuroimaging finding. Important late sequelae were present at 12 months of age.

Keywords: Cytomegalovirus, Descriptive Epidemiology, Hearing Impairment, Newborns.

RESUMO

Introdução: O citomegalovírus é um vírus amplamente disseminado, capaz de permanecer latente e reativar-se, com alta soroprevalência global. No Brasil, a soroprevalência supera 95%, com infecções primárias predominando na infância. **Objetivo:** Descrever o perfil clínico ao nascimento e o desfecho aos 12 meses de idade dos pacientes diagnosticados com infecção congênita pelo citomegalovírus em um hospital pediátrico referência de Florianópolis, no período de 2017 a 2022. **Métodos:** Tratou-se de estudo retrospectivo, observacional e descritivo, com análise de dados secundários. A pesquisa foi aprovada pelo Comitê de Ética em Pesquisa em Seres Humanos. **Resultados:** Dos 20 casos incluídos no estudo, 12 (60%) eram do sexo feminino, e todos de cor ou raça branca. Dos casos, 14/17 (82,3%) eram de nascimento a termo e 14/16 (87,5%) apresentavam peso ao nascer pequeno para a idade gestacional**.** Identificou-se icterícia em 7/13 (53,8%), microcefalia em 5/18 (27,7%), hiperbilirrubinemia conjugada em 5/8 (62,5%) e calcificações intracranianas em 9/20 (45%) prontuários. Foram reprovados na triagem auditiva neonatal 6/20 (30%) casos e 5/20 (25%) apresentaram perda bilateral ao potencial evocado auditivo de tronco encefálico. Aos 12 meses de idade, encontrou-se perda auditiva bilateral e microcefalia em 5/8 (62,5%) e 7/13 (53,8%) casos, respectivamente. **Conclusão:** Peso ao nascimento pequeno para a idade gestacional, icterícia e microcefalia foram alterações prevalentes. Calcificações intracranianas foram o achado de neuroimagem mais comum. Sequelas tardias importantes estiveram presentes aos 12 meses de idade.

Palavras-chave: Citomegalovírus. Epidemiologia descritiva. Deficiência auditiva. Recém-nascidos.

INTRODUCTION

Cytomegalovirus (CMV) is a virus capable of establishing latency within its host following the primary infection. Recurrent infections may arise either from reactivation of a latent infection or through reinfection by distinct viral strains[1]. CMV is ubiquitous, with soroprevalence rates ranging from below 50% in high-income countries to nearly 100% in developing countries[2]. In Brazil, the soroprevalence exceeds 95%, with most primary infections occurring during childhood[3].

Congenital CMV infection (cCMV) is the world's most prevalent intrauterine viral infection and constitutes the main cause of non-hereditary hearing loss[4-6]. The estimated global prevalence of cCMV ranges from 0.6 to 0.7%, with a Brazilian prevalence that varies considerably, ranging from 0.7% to 11%[7-9].

Only 10 to 15% of infants with cCMV are symptomatic at birth. Clinical manifestations overlap with those of other congenital infections and may include: petechiae, jaundice, hepatosplenomegaly, small for gestational age (SGA), microcephaly, lethargy, poor sucking reflex, haemolysis, viral pneumonia, chorioretinitis, seizures and sensorineural hearing loss (SNHL). Severe cases may present with sepsis and even death[5].

Vertical transmission may occur following a maternal primary infection, viral reactivation or reinfection with a different viral strain. Although vertical transmission is more likely after a maternal primary infection, nearly 90% of cCMV cases in Brazil arise from non-primary infections, due to the high maternal seroprevalence rate[10]. The risk of vertical transmission increases with advancing gestational age; the clinical manifestations of cCMV, however, tend to be more severe when the infection occurs in the early stages of intrauterine development[6].

Screening for gestational CMV remains controversial as assessing maternal seroconversion would only identify primary infection,

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failing to detect vertical transmission arising from viral reactivation or maternal infection by different viral strains. Furthermore, most clinical guidelines concur that there are no effective interventions available to prevent vertical transmission of CMV[4,6,11,12].

After birth, the diagnosis of cCMV is preferably made through viral RNA identification in the newborn's urine or saliva samples within the first 21 days of life. Beyond this time frame, it becomes difficult to distinguish congenital infection to postnatal infection. After diagnosis, treatment with intravenous ganciclovir is the choice for symptomatic infants, aiming to prevent further sequelae[10-13].

OBJECTIVE

Considering cCMV high prevalence and its potential severity, this study aims to describe the epidemiological and clinical profiles of infants diagnosed with cCMV and assessed from January 2017 to December 2022 at a paediatric tertiary hospital in the state of Santa Catarina. The study aims to provide data that improve the understanding of cCMV among healthcare providers, promoting timely diagnosis and adequate treatment in order to reduce morbidity and mortality. Furthermore, the findings may support the development of better public health policies for follow-up and care of patients.

METHODS

This is a retrospective, observational and descriptive study based on data obtained from electronic medical records of patients evaluated between January 2017 to December 2022 at a paediatric tertiary hospital in the city of Florianopolis. The study was approved by the institution's Human Research Ethics Committee under the identification number 6.310.165.

All patients diagnosed with cCMV, evaluated in the previously mentioned time frame until 2 incomplete years of age and identified in the electronic medical record with the ICD-10 code P35.1 (congenital cytomegalovirus infection) were included in the study.

Patients without laboratory confirmation of the diagnosis, those in whom cCMV was ruled out in further investigation and cases in which the infection was most likely acquired postnatally were excluded from the study.

The following variables were assessed:

- Demographic and socioeconomic (sex, skin colour according to the IBGE classification[14], city of origin according to the IBGE classification in mesoregions[15]);
- Prenatal data (maternal age, number of antenatal care visits, other infections in the gestational period);
- Perinatal data (gestational age at birth, weight and head circumference at birth according to the WHO classification[16]; Apgar score at 5 minutes of life);
- Neonatal clinical manifestations (petechiae, jaundice, hepatosplenomegaly, microcephaly, hypotonia, chorioretinitis);
- Laboratory findings (haemolytic anemia, elevated serum aminotransferases and bilirubin, thrombocytopenia, elevated cerebrospinal fluid protein count);
- Imaging findings (intracranial calcifications, white matter abnormalities, ventriculomegaly);
- Universal hearing screening and auditory brainstem evoked response (ABR) results;
- Administration or not of ganciclovir and time of treatment;
- Specialized follow-up (neonatologist, neurologist, infectious diseases specialist)
- Sequelae at 12 months of age (epilepsy, hearing loss, microcephaly).

Data were gathered from electronic medical records and tabulated using *Google Sheets*®. Median, mean and standard deviation were used to describe quantitative variables; frequency and percentage were calculated for qualitative variables. Results were subsequently presented in descriptive tables.

RESULTS

42 patients were initially identified and 20 (47.6%) were included in the final study after the exclusion criteria were applied. The identified male to female rate in the sample was 2:3. All patients were identified as having white skin and 12 (60%) originated from the Great Florianopolis mesoregion. The sample also included infants from the West (15%), Mountains (10%), Itajai Valley (10%) and North (5%) mesoregions.

Regarding maternal and prenatal data, maternal age was recorded in 12 medical records, of which 4 (33.3%) mothers were under 21 years of age. The number of prenatal visits was noted in 7 records (4, 5, 5, 7, >10 [not quantified], 11, and 12), with fewer than 6 visits in 3 (42.8%) of these.

Maternal sexually transmitted diseases (STDs) were identified in 3 (15%) cases, one case each of human immunodeficiency virus (HIV), syphilis and hepatitis C. Information regarding maternal STDs was not recorded in 4 (20%) cases.

Regarding perinatal data, gestational age (GA) at birth was recorded in 17 medical records, of which 14 (82.3%) were born at term. Weight at birth was recorded in 16 medical records, with 14 (87.5%) infants classified as SGA and the remaining 2 (12.5%) presented appropriate weight for gestational age (AGA). Apgar score at 5 minutes of life was available in 15 cases, with a mean of 8.8 [0.76 (7-10)] and median of 9. The remaining data are presented in Table 1.

With regard to neonatal clinical findings, jaundice was identified in 7/13 (53.8%) infants, hepatomegaly and/or splenomegaly in 5/13 (38.4%) and microcephaly in 5/18 (27.7%).

Among the laboratory findings, anemia was registered in 2/8 (25%) cases and an increase in serum direct bilirubin was found in 5/8 (62.5%) infants. Cerebrospinal fluid puncture was performed in only 1 (5%) case of the sample, in which the protein count was elevated. Clinical and laboratory findings are presented in Table 2.

With regard to radiologic findings, intracranial calcifications, white matter abnormalities and ventriculomegaly were found in 9 (45%), 8 (40%) and 2 (10%) cases, respectively.

The laboratory diagnostic method was serological in 11 (55%) cases, urinary RT-PCR in 7 (35%) and serum RT-PCR in 1 (5%). The diagnostic method was not described in 1 case of the sample, as the patient had been diagnosed in the maternity unit prior to hospital transfer, and no details regarding the diagnostic method were recorded in the medical notes. With regard to the audiological evaluation, 6 (30%) infants did not pass the universal hearing screening with otoacoustic

emissions (OAEs), and 2 out of these presented bilateral failure. ABR testing was performed in 10 (50%) infants, of whom 5 presented bilateral SNHL. ABR was not performed in 4 (20%) cases, and no information regarding ABR was available in 6 (30%) medical records.

Table 1. Demographic, prenatal, and perinatal data of cytomegalovirus-infected patients treated at a tertiary pediatric hospital in Florianópolis (SC), from 2017 to 2022.

	n/N (%)
Female	12/20 (60)
White skin	20/20 (100)
Mesoregion of origin	
Great Florianópolis	12/20 (60)
West	3/20 (15)
Mountains	2/20 (10)
Itajaí Valley	2/20 (10)
North	1/20 (5)
Maternal age <21 years	4/12 (33.3)
Antenatal care <6 consultations	3/7 (42.8)
Maternal STDs	
HIV	1/20 (5)
Syphilis	1/20 (5)
Hepatitis C	1/20 (5)
None	13/20 (65)
Ignored	4/20 (20)
Gestacional age at birth	
Preterm	3/17 (17.6)
Term	14/17 (82.3)
Apgar score at 5 minutos (N=15)	8,8 [0.76 (7–10)]

STI: sexually transmitted infections; HIV: human immunodeficiency virus. Source: Authors, 2024.

Table 2. Clinical findings and laboratory abnormalities in cytomegalovirus-infected patients treated at a tertiary pediatric hospital in Florianópolis (SC), 2017–2022.

	n/N (%)
SGA	14/16 (87.5)
Petechiae	1/13 (7.6)
Jaundice	7/13 (53.8)
Microcephaly	5/18 (27.7)
Hypotonia	5/15 (33.3)
Hepatomegaly and/or splenomegaly	5/13 (38.4)
Chorioretinitis	3/17 (17.6)
Seizures in first year of life	4/15 (26.6)
Anemia	2/8 (25)
Leukopenia	0/8 (0)
Neutropenia	0/8 (0)
Thrombocytopenia	2/8 (25)
Increase in serum aminotransferases	
AST	3/7 (42.8)
AST+ALT	2/7 (28.5)
Absent	2/7 (28.5)
Increase in serum direct bilirubin	5/8 (62.5)
Increase in cerebrospinal fluid protein	1/1 (100)

SGA: small for gestational age; AST: aspartate aminotransferase; ALT: alanine aminotransferase; DB: direct bilirubin.Source: The authors, 2024.

During the neonatal period, treatment with ganciclovir was applied to 6 (30%) cases, of whom 4 received the medication for the minimal recommended duration of 42 days. Myelotoxicity secondary to ganciclovir was not reported in the study sample.

Other congenital infections were described in 2 (10%) neonates, those being 1 case of syphilis and 1 of hepatitis C each. A minimum of one outpatient consultation was recorded in 13 (65%) cases with infectious diseases, 12 (60%) cases with neurology and 3 (15%) cases with neonatology, respectively.

During follow-up, 4/15 (26.6%) infants developed some form of epilepsy within the first year of life. At 12 months of age 5/8 (62.5%) cases presented bilateral SNHL diagnosed via ABR, and 7/13 (53.8%) presented with microcephaly. Out of the 9 cases that presented microcephaly or SNHL at 12 months of age, 7 (77.7%) had not received ganciclovir for the minimum recommended duration. Clinical outcomes at 12 months of age are presented in Table 3.

At 24 months of age, 13 (65%) cases had follow-up consultations at the institution, 5 (25%) had been discharged from outpatient follow-up, and 2 (10%) infants were lost to follow-up. No deaths were reported in the study time frame.

DISCUSSION

The most prevalent clinical findings in the sample were small for gestational age birth weight, jaundice, microcephaly, hypotonia, and hepato and/or splenomegaly. These findings are consistent with previous studies involving patients with symptomatic cCMV infection at birth. However, the presence of petechiae, which is described in the literature as occurring in 50–75% of cases, was identified in only 1 out of 13 cases (7.6%) in the present study. This may be related to the transient nature of this sign, which may not have been visible during physical examination at the time of outpatient visits[17-19].

In the present study, 7 out of 13 cases (53.8%) presented with microcephaly at 12 months of age, including one infant who had a normal head circumference at birth. During the first year of life, 4 out of 15 children (26.6%) also developed some form of epilepsy. These findings are consistent with previous literature, which reports long-term microcephaly in approximately 37% and epilepsy in 23% of cCMV cases. Other late-onset sequelae described include intellectual disability, strabismus, and chorioretinitis, establishing cCMV as the leading viral cause of neurodevelopmental delay[19-21].

Among the laboratory abnormalities, signs of reticuloendothelial involvement - such as elevated direct bilirubin, increased serum

Table 3. Unfavorable clinical outcomes at 12 months of age in patients with cytomegalovirus attended at a tertiary pediatric hospital in Florianópolis (SC), from 2017 to 2022.

	n/N (%)
Hearing loss	
Normal	3/8 (37.5)
Bilateral loss	5/8 (62.5)
Unilateral loss	0/8 (0)
Microcephaly	7/13 (53.8)
Seizures in the first year of life	4/15 (26.6)

Source: The authors, 2024.

transaminases, and anemia - were the most common findings, which is also consistent with previous studies[21]. Less frequent findings described in earlier works, such as leukopenia and neutropenia, were not observed in the present sample[17-19].

In the sample, 6 (30%) patients failed the hearing screening with OAE and 5 (25%) exhibited bilateral hearing deficit on ABR. Of the 8 patients who underwent follow-up ABR at 12 months of age, bilateral hearing loss was observed in 5 (62.5%), all of whom had already shown some alteration in the newborn hearing screening. This finding underscores the importance of neonatal hearing screening in this population.

SNHL is the most common late sequela of cCMV, and its early identification allows the implementation of non-pharmacological interventions that can reduce the functional impairment associated with hearing loss, thereby supporting speech and language development. SNHL in cCMV cases may be progressive or have delayed onset, highlighting the need for audiological follow-up during the early years of life - even in those with normal OAE and ABR at birth[21,22].

Ganciclovir therapy is indicated for symptomatic cCMV cases and should be initiated within the first month of life. Nevertheless, due to delays in diagnosis, treatment was administered in only 6 cases (30%), and only 4 of these received the medication for the minimum recommended duration of 6 weeks. In a randomized clinical trial conducted in the United States involving 100 neonates with symptomatic cCMV, Kimberlin et al. found better audiological outcomes at 6 months of age in patients who received ganciclovir compared to those who received placebo[23].

More recently, considering that SNHL may have a late onset, Kimberlin et al. compared valganciclovir treatment administered for 6 weeks versus 6 months, evaluating hearing loss and neurodevelopmental outcomes. Although no difference was found in audiological outcomes at 6 months of age between the two groups, the 6-month antiviral therapy showed better neurodevelopmental results[24]. Based on these data, international guidelines recommend oral valganciclovir for 6 months in symptomatic cCMV cases. However, in Brazil, only intravenous ganciclovir is available through the country's public health system[10,11].

There is still insufficient evidence regarding antiviral therapy in asymptomatic cCMV patients, as only small studies have been conducted with this population to date. Therefore, pharmacological treatment is not indicated in these cases. Foscarnet and Cidofovir are second-line drugs that may be recommended in special situations of viral resistance and/or intolerance to ganciclovir, in which case follow-up by a pediatric infectious disease specialist is advised[21,25].

Although cCMV and its sequelae represent a significant public health problem, universal neonatal screening programs have not been implemented, partly because an appropriate diagnostic method for a population screening program has not yet been established. Dollard et al.[13] published a cohort study in 2021 involving 12,554 newborns, which evaluated the use of RT-PCR on dried blood spot samples for cCMV diagnosis. A sensitivity of 87.5% was identified, indicating the feasibility of using this test in a potential screening program, especially in countries like Brazil, where a complex infrastructure for universal neonatal screening is already in place[13,26].

In the sample, the number of prenatal visits was recorded in only 7 medical records, of which 3 cases had an insufficient number of visits [27]. This highlights the importance of adequate prenatal and periconceptional care, as simple behavioral hygiene measures, such as frequent handwashing, have proven effective as primary prevention of cCMV[4,28].

The administration of Valaciclovir to pregnant women has gained attention in recent years as a medication with potential for preventing cCMV. In a double-blind randomized clinical trial, Shahar-Nissan et al. evaluated the efficacy of Valaciclovir in preventing fetal cytomegalovirus infection during the first trimester in cases of primary maternal infection, identifying a 71% reduction in vertical transmission compared to placebo[27]. A 2023 meta-analysis including a total sample of 527 patients reaffirmed these findings[29]. Valaciclovir use has also been studied as a treatment during pregnancy for fetuses infected with CMV. Leruez-Ville et al. reported a higher rate of patients without central nervous system abnormalities at birth following valaciclovir treatment, who remained asymptomatic during 12 months of follow-up [30].

Study strenghts

The findings of the cited studies suggest potential for revising the current understanding of gestational CMV screening, indicating the possibility of new approaches to managing maternal-fetal infection. In this context, conducting studies with robust scientific methodology is essential to deepen knowledge about the effectiveness of screening and intervention strategies, thereby contributing to the evolution of recommendations and improving maternal-fetal outcomes.

Limitations

The limitations of our study are intrinsic to its retrospective design and the use of secondary data. Given the importance of the topic, the authors suggest further prospective studies, especially involving the Brazilian population, to evaluate strategies for preventing vertical transmission, treatment of affected neonates, measures to reduce their long-term adverse effects, and the effectiveness of maternal and neonatal screening programs.

CONCLUSION

Therefore, the present study concluded that important prenatal follow-up data, such as maternal age and number of visits, were missing in the majority of medical records. Other maternal STIs, including HIV, syphilis, and hepatitis C, were identified. Most of the sample consisted of term newborns with SGA birth weight. Jaundice, hepato - and/or splenomegaly, hypotonia, and microcephaly were the most prevalent clinical findings. The most frequent laboratory abnormality was elevated direct bilirubin. Intracranial calcifications and white matter changes were the most common radiological findings. Intravenous ganciclovir treatment for the minimum duration of 6 weeks was administered in a minority of cases. Significant late sequelae were present at 12 months of age, including bilateral hearing loss and microcephaly.

Author contributions

BB: Formal analysis, Conceptualization, Data curation, Writing – review and editing. IGFN: Writing – review and editing. ERC: Formal analysis, Conceptualization, Writing – review and editing.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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