Late sequelae of congenital cytomegalovirus infection – The urgency of a neonatal approach

Sequelas tardias de infeção congénita por citomegalovírus – A urgência de uma abordagem neonatal

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ABSTRACT

Introduction: Congenital cytomegalovirus (CMV) infection is the main cause of sensorineural deafness in children. In Portugal, routine screening of the infection during pregnancy is not performed. It is acknowledged that late sequelae may occur in children with congenital infections, even when they are asymptomatic at birth. The aim of this study was to investigate early and late sequelae in children of mothers with positive CMV immunoglobulin (Ig) M and IgG during pregnancy.

Materials and Methods: Patients: Children born to mothers with positive CMV IgM and IgG during pregnancy at a Portuguese tertiary hospital between August 2006 and August 2020. Demographic, clinical, and laboratory variables and early and late sequelae were retrospectively assessed. Late sequelae included delayed psychomotor development, sensorineural deafness, and vision changes.

Results: In the last 14 years, 31 newborns were born to mothers with positive IgM and IgG during pregnancy in the considered hospital (0.08% of the total number of births). CMV infection was confirmed in six of these children (19.4%), of whom one was symptomatic at birth, with multiorgan involvement, and died at the age of four months. Late sequelae were observed in one patient, specifically learning disabilities and attention-deficit/hyperactivity disorder. No cases of ophthalmological or otorhinolaryngological alterations were identified.

Discussion: Although congenital CMV infection is a potentially fatal condition, only one death was reported in the present study sample. Late sequelae were also only observed in one case, which was asymptomatic at birth.

Conclusion: These results suggest that the indications for CMV screening during the neonatal period should be reassessed. This is particularly important in asymptomatic newborns, as a way to implement early treatment and prevent late sequelae.

Keywords: complication; cytomegalovirus infection; diagnosis; neurodevelopmental disorder

RESUMO

Introdução: A infeção congénita por citomegalovírus (CMV) é a principal causa de surdez neurosensorial na infância. Em Portugal, o rastreio na grávida não é realizado por rotina. Sabe-se que podem ocorrer sequelas tardias em crianças com infeção congénita, mesmo quando são assintomáticas ao nascimento. O objetivo deste estudo foi investigar a ocorrência de sequelas precoces e tardias em crianças com mães com imunoglobulina (Ig)M e IgG positiva para CMV durante a gravidez.

Materiais e Métodos: Participantes: Crianças nascidas de mães com IgM e IgG positiva para CMV durante a gestação num hospital terciário português entre agosto de 2006 e agosto de 2020. Foram retrospectivamente avaliadas variáveis demográficas, clínicas e laboratoriais, bem como sequelas precoces e tardias. Foram consideradas sequelas tardias atraso no desenvolvimento psicomotor, surdez neurosensorial e alterações da visão.

Resultados: Nos últimos 14 anos, foram identificados no hospital considerado 31 casos de recém-nascidos de mães com IgM e IgG positiva para CMV durante a gravidez.
INTRODUCTION

Cytomegalovirus (CMV) is the most frequent etiological agent of congenital infections and the most common cause of non-genetic sensorineural hearing loss in children. It is also an important cause of congenital malformations and delayed psychomotor development. With an estimated incidence of 0.7% (0.2-2%), CMV infection is the most prevalent congenital infection in developed countries. In Portugal, two studies with a ten-year gap reported different prevalences of the infection – 1.05% in 2009 and 0.007% in 2019 –, and the second national serological survey conducted in 2001-2002 reported a seropositivity rate of 76.7-81.5% in women aged 15-44 years.

Vertical transmission can occur via transplacental route, with a reported primary infection rate (infection in a seronegative mother) of 30-35% and a secondary infection rate (reinfection or reactivation in a seropositive mother) of 1.2%. Worst outcomes are reported if the infection occurs in the first pregnancy trimester in mothers with no previous contact with the virus (i.e., seronegative). Viral transmission can also occur through secretions, with recent literature documenting transmission via breast milk.

The clinical presentation is variable. About 10-15% of infected newborns (NB) are symptomatic at birth. Severe infection is less frequent and characterized by involvement of the central and reticuloendothelial nervous systems. The most frequent signs of CMV infection are intrauterine growth restriction (IUGR), low birth weight for gestational age, microcephaly, petechial rash, jaundice, hepatosplenomegaly, and intracranial calcifications. Late sequelae may include sensorineural deafness and mental retardation.

Late sequelae in NB asymptomatic at birth are a growing concern. Some authors suggest an incidence of 13.5%, with sensorineural deafness being the most common outcome. Learning disabilities, low vision acuity, and neurodevelopmental delay have also been described.

Currently, there are no recommendations for systematic CMV screening during pregnancy or neonatal period. In Portugal, the Directorate-General of Health (DGS) recommends serological screening in the preconception period. In case of suspicion, this allows a comparison between laboratory values and facilitates diagnostic procedures. Serology is performed in cases of obstetric findings suggestive of fetal infection, as IUGR, microcephaly, hydrocephalus, or hepatic or brain calcifications. However, the infection is often asymptomatic in healthy adults and most fetuses have no manifestations.

The aim of this study was to assess the epidemiology of congenital CMV infection in a Portuguese tertiary hospital and its early and late complications in NB born to mothers with positive IgG and IgM during pregnancy, including cases symptomatic and asymptomatic at birth.

MATERIALS AND METHODS

This was a retrospective cohort study of NB born to mothers with positive CMV IgG and IgM during pregnancy at a Portuguese tertiary hospital with about 2500 births/year over a 14-year period (between August 1, 2006 and August 1, 2020).

NB testing for congenital CMV was performed up to 21 days postnataally through study of the virus in urine (viruria) or in peripheral blood (through polymerase chain reaction [PCR]).

All NB born to mothers with positive CMV IgG and IgM during pregnancy were clinically monitored at the Neonatology outpatient clinic of the study hospital or at the hospital of residence until the age of two years. After that period, follow-up was maintained at pediatric outpatient clinic setting. Cranial ultrasound and developmental assessment were carried out, and clinical surveillance in Otorhinolaryngology and Ophthalmology was performed for a maximum of 14 years. In cases of laboratory-confirmed congenital infection, NB were also monitored in a neurodevelopmental outpatient clinic.

Demographic and clinical data were retrieved, as well as data...
RESULTS

A total of 38,294 births were reported in the last 14 years in the considered tertiary hospital, of which 31 (0.08%) to mothers with positive CMV IgG and IgM. The infection probably occurred in the first pregnancy trimester in 12 cases (38.7%), in the second trimester in seven cases (22.6%), and in third trimester in nine cases (29.0%). In three cases, it was not possible to ascertain the trimester in which the infection occurred.

CMV screening during pregnancy was driven by ultrasound changes in four cases (12.9%). Three had a single ultrasound anomaly – IUGR (1), liver and intestinal calcifications (1), and brain calcifications (1) – and the fourth had several changes in serial prenatal ultrasound scan, including intestinal hyperechogenicity since 19 weeks, long bones < P5, microcephaly, and severe IUGR with flowmetry changes in the umbilical arteries and middle cerebral artery since 23 weeks. In the remaining 27 cases (87.1%), the reason for CMV screening could not be determined.

The median gestational age at birth was 39 weeks (range 33-41 weeks). Two NB (6.5%) had low birth weight for gestational age, and 17 (54.8%) were female.

Viruria was performed in 29 NB (93.5%), by shell vial microculture until 2015 and PCR since then. In two cases, PCR was done in peripheral blood. A definitive diagnosis of congenital infection was established for six NB (19.4%). The incidence of congenital infection was 15.7/100,000 live births. All these diagnoses were established by positive viruria, with a median of 50,921,017/uL copies (range 33,323-69,578,841/uL; Table 1).

Five of six NB (83.3%) with confirmed infection were asymptomatic at birth, including the three NB with findings in prenatal ultrasound scan. During follow-up (lasting between four months and 14 years), one child showed late sequelae. The mother had positive CMV IgM and IgG in the second pregnancy trimester and no changes in prenatal ultrasound, and although the child was asymptomatic at birth, learning difficulties detected upon starting school prompted the diagnosis of attention-deficit/hyperactivity disorder. The remaining four children who were asymptomatic at birth showed no changes in ultrasound scan, nor neurodevelopmental, auditive, or vision deficits.

Only one child was symptomatic at birth, with alterations in serial prenatal ultrasound scans and multisystemic involvement with hyponxia, microcephaly, cholestatic hepatitis, coagulopathy and bilateral hyerechogenicity, and lenticulostriate vasculopathy on cranial ultrasound. This child was treated with ganciclovir until the 20th day of life, and with valganciclovir subsequently. During follow-up, severe feeding difficulties and delayed psychomotor development were noted, and the child suddenly died at the age of four months.

Table 1 - Cases of congenital CMV infection in the present study

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Sex</th>
<th>Positive CMV IgM and IgG</th>
<th>Prenatal ultrasound</th>
<th>Diagnosis</th>
<th>Clinical status at birth</th>
<th>Treatment at birth</th>
<th>Late sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 weeks</td>
<td>Female</td>
<td>1st trimester</td>
<td>Multiple alterations*</td>
<td>Viruria</td>
<td>Serious clinical condition</td>
<td>Ganciclovir</td>
<td>Feeding difficulty, psychomotor impairment. Death at 4 months</td>
</tr>
<tr>
<td>40 weeks</td>
<td>Female</td>
<td>2nd trimester</td>
<td>No alterations</td>
<td>Viruria</td>
<td>Asymptomatic</td>
<td>No</td>
<td>Learning difficulties; ADHD</td>
</tr>
<tr>
<td>40 weeks</td>
<td>Female</td>
<td>3rd trimester</td>
<td>No alterations</td>
<td>Viruria</td>
<td>Asymptomatic</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>39 weeks</td>
<td>Male</td>
<td>3rd trimester</td>
<td>No alterations</td>
<td>Viruria</td>
<td>Asymptomatic</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>37 weeks</td>
<td>Male</td>
<td>2nd trimester</td>
<td>No alterations</td>
<td>Viruria</td>
<td>Asymptomatic</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>35 weeks</td>
<td>Male</td>
<td>2nd trimester</td>
<td>No alterations</td>
<td>Viruria</td>
<td>Asymptomatic</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; CMV, cytomegalovirus; IgG, immunoglobulin G; IgM, immunoglobulin M

*Microcephaly with delayed cerebral sulcation; enlarged subarachnoid space; severe fetal growth restriction; hyperechogenic fetal bowel; renal hypoplasia with lack of differentiation
DISCUSSION

Congenital CMV infection remains a neonatal concern. A definitive diagnosis of congenital CMV infection was established in this study in six of 31 infants born to mothers with positive IgM and IgG during pregnancy, which represents an incidence of 16 per 100,000 births. This is higher than the last known reported incidence between 2006 and 2011 of 7 per 100,000 births.\(^{(1)}\)

In this study, maternal infection in cases of congenital CMV infection mainly occurred in the second and third pregnancy trimesters. Only in one case of seroconversion occurred in the first trimester, with severe presentation at birth. Several studies suggest that the placenta is a means of transmission not only in early stages of pregnancy.\(^{(13)}\) Placental infection directly contributes to the pathophysiology of congenital infection by compromising its formation, resulting in placental failure.\(^{(13,14)}\) Placental pathology is strongly associated with fetal and neonatal disease.\(^{(14)}\)

Late sequelae were observed in one of six children with infection confirmed at birth in this analysis. No cases of sensorineural deafness, the most frequently described late sequela in the literature, were reported. Delayed psychomotor development is also a common late sequela in initially asymptomatic NB, which may only become noticeable at school age.\(^{(14)}\) One possible explanation is the absence of a neonatal diagnosis at birth in asymptomatic children. In the present study, this diagnosis was performed early due to the continuous monitoring of NB with a history of mothers with positive CMV IgG and IgM during pregnancy, even if asymptomatic at birth.

Concerns regarding CMV congenital infection have been growing, particularly due to the overall lack of awareness of the infection among the general population. A study from 2019 in the United States showed that only 20% of 726 women of childbearing age (18-44 years) were aware of the infection.\(^{(15)}\) While CMV may be considered a mostly harmless virus, it can have relevant sequelae. One death related to a severe case of infection was found in this study, and the literature describes 5-10% of deaths due to congenital CMV infection.\(^{(11)}\)

Not less relevant is the fact that the disease is probably underdiagnosed.\(^{(16)}\) In a recent Italian study that investigated the presence of CMV on the Guthrie card of children with altered otoacoustic emissions, 6.1% were found to be positive for the virus.\(^{(17)}\) All children had been born from pregnancies with no previously identified complications and were asymptomatic at birth.

The gold standard for diagnosing congenital CMV infection is its identification in urine in the first three weeks of life. However, since 80-90% of NB with the infection are asymptomatic, they are not tested for CMV.\(^{(18)}\) Since 10-15% of asymptomatic NB develop late sequelae and early treatment is highly efficacious, there is an urgent need for a global screening strategy of CMV congenital infection.\(^{(27)}\)

Several groups are already investigating this issue in an effort to provide solutions. Some suggest to include CMV testing on the Guthrie card, which has a reported sensitivity of 71-100%.\(^{(15)}\) Others suggest to test the NB’s saliva in the first hours of life, which has a sensitivity no lower than viruria and the advantages of being a faster and non-invasive method.\(^{(19)}\) Universal screening of NB can be an important step in detecting CMV infection in asymptomatic children and would enable earlier follow-up and the possible detection of late sequelae.

The small sample size is a limitation of this study that should be acknowledged. In addition, multicentre, cost-effective studies can be decisive in setting up a strategy for control and screening of CMV infection, a condition with potentially significant sequelae. Until then, the authors suggest to monitor NB who came into close contact with CMV during pregnancy until they reach school age, even if asymptomatic at birth.

CONCLUSION

Congenital CMV infection is a potentially serious condition that can be fatal. Not only symptomatic, but also asymptomatic cases at birth are relevant, due to the possibility of late sequelae. Longer surveillance and monitoring of these children and even a review of the indications for CMV screening in pregnant women or NB seem justified.

AUTHORSHIP

Teresa Botelho: Conceptualization; Data curation; Formal Analysis; Investigation; Methodology; Visualization; Writing –original draft; Writing – review & editing

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Ana Rodrigues Silva: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – review & editing

REFERENCES


3. Vide Tavares M, Domingues AP, Tavares M, Malheiro E, Tavares F, Moura P. Citomegalovirus: Existe lugar para o rastreio durante a...


