Congenital cytomegalovirus infection in an extremely preterm newborn exposed to chemotherapy in utero

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Abstract

Cytomegalovirus (CMV) infection is the most frequent congenital infection in developed countries and the main cause of non-hereditary sensorineural deafness.

We report the case of a 27-week-old newborn (NB) with symptomatic congenital CMV infection. The pregnancy was monitored and CMV seroconversion was detected in the first trimester maternal serum screening. At 10 weeks of gestation the mother was diagnosed with breast carcinoma, submitted to a tumorectomy at 17 weeks and started chemotherapy by the 21st week. CMV fetal infection was confirmed by positive DNA detection in amniotic fluid at 21 weeks of gestation. The mother received valaciclovir therapy from the 22nd week of pregnancy until delivery.

The NB was delivered by cesarean section at 27 weeks with a birth weight of 950 g. In the first day of life, the NB suffered severe thrombocytopenia and congenital CMV infection was confirmed by positive PCR for CMV DNA in both urine and blood samples. The NB completed six weeks of ganciclovir treatment with progressive clinical and analytical recovery. Auditory evoked potentials were absent in the left ear. On the 84th day of life, the infant, due to clinical and laboratory assessments deterioration, started valganciclovir, completing a total of 6 months of treatment. Currently, at 36 months, the infant presents an appropriate development for the corrected age and has no indication for cochlear implantation.

The authors intend to point out the difficulty of treating this infection associated with a high morbimortality, as there is no definitive evidence about the potential benefit of fetal infection treatment during pregnancy, the evidences regarding the effectiveness of antiviral therapy in NB refer to a restricted group of NBs, and this therapy may be associated with important
side effects. In this case, the existence of other factors that increase the NB vulnerability and potential sequelae make decisions even more difficult.

Keywords
Congenital infection, cytomegalovirus, deafness, extreme prematurity, maternal chemotherapy.

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How to cite

Introduction
Cytomegalovirus (CMV) is a ubiquitous DNA virus belonging to the Herpesviridae family [1]. CMV infection is distributed worldwide and is the most common congenital infection in developed countries (prevalence of 0.6%) and the leading cause of sensorineural hearing loss (SNHL) [2-4]. Portugal has one of the highest prevalence of congenital CMV infection in Europe (1.05%) [5].

During pregnancy, the infection often results from the contact of the pregnant woman with young children [1]. Congenital infection may occur independently of the trimester of pregnancy when the mother is infected, but severe sequelae are most often associated with maternal infection acquired during the first half of gestation [1].

Congenital CMV infection has high morbidity [6]. Most of the newborns (NBs) infected are asymptomatic, however about 10% present symptoms [1, 3]. The most important and frequent consequence of congenital CMV infection is SNHL [1, 3, 7], which occurs in about 50% of symptomatic NBs and 15% of asymptomatic NBs [1, 4, 8]. This infection may also be associated with other long-term neurological problems such as cerebral palsy, mental retardation, seizures and visual impairment. SNHL resulting from CMV infection may not be detected in NB hearing screening in more than half of the cases, since hearing loss is frequently fluctuant and progressive [1, 3, 9, 10]. In most cases, it develops during the first year of life [10]. Therefore, in some cases of congenital infection, symptoms are detected after some years after birth and it is difficult to determine its aetiology. Although diagnosis of congenital CMV infection requires virus detection in body fluids collected during the first three weeks of life, retrospective diagnosis is possible through detection of CMV DNA by polymerase chain reaction (PCR) in blood stored on Guthrie cards [7]. Some authors advocate universal screening of CMV congenital infection in NBs in order to allow for the early identification of infected children and intervention when appropriate [9-11]. As the analysis of CMV DNA in blood stored on Guthrie cards appears to have a low sensitivity [12], the collection of saliva or urine may be an alternative [13, 14].

We present the case of an extremely preterm NB, exposed to chemotherapy in utero, with congenital CMV infection, and discuss his treatment and the main difficulties faced.

Case report
First born from young parents (mother 29 years old, father 30 years old). The pregnancy was monitored and CMV seroconversion was detected in the first trimester maternal serum screening (7 weeks of pregnancy). At 10 weeks of gestation the mother was diagnosed with breast carcinoma (invasive ductal carcinoma, G2 grade of differentiation). She was submitted to a tumorectomy at 17 weeks of gestation and started chemotherapy (epirubicin, cyclophosphamide and 5-fluorouracil) at 21 weeks that lasted until the end of pregnancy (2 cycles of chemotherapy, the second cycle was performed about 1 week before delivery). At 21 weeks of gestation, amniotic fluid samples were collected and CMV fetal infection was demonstrated by positive DNA detection. The mother received valaciclovir therapy (8 g/day, 4 doses/day) from 22 weeks of gestation until delivery (27 weeks and 3 days). Fetal ultrasound revealed normal fetal growth and development. At 26 weeks, due to changes in umbilical flow, a corticosteroid cycle was carried out.

The NB was delivered by cesarean section at 27 weeks with a birth weight of 950 g (weight appropriate for his gestational age) and was admitted to the neonatal intensive care with non-invasive ventilatory support by continuous positive airway pressure. The NB examination revealed prematurity signs and presence of petechiae.
Blood tests confirmed severe thrombocytopenia (32,000/ul). Congenital CMV infection was confirmed by positive PCR for CMV DNA in the urine and by the presence of 5.8 x 10^5 copies/ml in the blood. Intravenous ganciclovir (6 mg/kg/day, 2 doses/day) was started on the 1st day of life, the dose being reduced by half on the 19th day due to thrombocytopenia (16,000/ul) and severe neutropenia (290/ul). No response was obtained bilaterally in the spontaneous otoacoustic emissions test. No waves with left ear stimulation were identified and thresholds of 40 dB were detected on the right ear in the auditory evoked potentials. Chorioretinitis was excluded by ophthalmology. The transfontanellar ultrasound suggested periventricular leukomalacia and the cerebral magnetic resonance imaging revealed the presence of two small rounded areas with hyposignal in gradient echo on the wall of the lateral ventricle body and on the left wall of the fourth ventricle, possibly corresponding to calcifications. The NB completed 6 weeks of treatment with progressive clinical and analytical recovery (PCR DNA for CMV in the blood less than 500 copies/ml).

On the 84th day of life the infant developed moderate thrombocytopenia (58,000/ul), cholestasis (TB 9.01 mg/dL, DB 4.93 mg/dL) and hepatic cytolysis (TGO 621 UI/L, TGP 188 UI/L). After excluding other causes of infections, the hypothesis of recurrence of CMV infection was considered and the infant started treatment with oral valganciclovir (16 mg/kg/dose, 2 doses/day). At that time CMV viral load was increased (47,000 x 10^4 copies/ml). With the beginning of treatment there was a clinical and laboratory improvement and CMV DNA became undetectable in blood by the end of the 1st month. The NB completed 6 months of therapy as outpatient.

He was referred to the cochlear implant unit. Due to his hearing levels, good cognitive performance and language acquisition, cochlear implantation was not indicated.

Currently, at 36 months of age, the child presents psycho-motor development adjusted to the corrected age (Griffiths scale – global development quotient 96.92) and remains without indication for cochlear implantation.

Discussion

Chemotherapy during pregnancy for the treatment of maternal cancers has become more acceptable in the past decade, however the period of pregnancy during which the fetus is exposed to chemotherapy seems to be critical. Chemotherapy after the first trimester of pregnancy – the period of fetal organogenesis – does not result in a higher incidence of congenital malformations [15, 16]. Amant et al. in a multicentre observational cohort study demonstrated, through long-term follow-up of children exposed to prenatal chemotherapy, that fetal exposure to chemotherapy in the second and third trimester of pregnancy was not associated with increased central nervous system or auditory morbidity [17].

In this case report, one could question the role that maternal chemotherapy could have had through maternal and fetal immunosuppression in the transmission of CMV infection. However, once the beginning of maternal chemotherapy and the diagnosis of fetal infection happened at the same time, this hypothesis was excluded. The authors speculate whether the very close chemotherapy cycle to the delivery, and the difficult drug elimination by the NB due to hepatic and renal immaturity associated with prematurity, could have contributed to NB immunosuppression [18, 19] and, consequently, for the development of symptoms related with the congenital infection.

Fetal CMV infection treatment during pregnancy, to prevent or reduce the severity of associated symptoms, has always been debatable as to its efficacy and potential adverse effects. Management options include therapy with CMV hyperimmunoglobulin (IGg-CMV) or antiviral drugs. IGg-CMV to prevent transmission from mother to fetus has produced conflicting results [20, 21]. Two randomized placebo-controlled phase III trials are currently underway in the United States and Europe to understand the role of IGg-CMV in the prevention of fetal infection. Regarding antiviral drugs, a pilot observational study has shown that the use of valaciclovir in pregnancy raises its concentration in the fetus to therapeutic plasma concentrations, with a decrease in viral load and absence of teratogenic effects. However, this study failed to determine the impact of the therapy on the neonatal disease [22]. The preliminary report of a recently published open-label multi-centre phase II study indicates that treatment of congenital CMV infection in utero, with high doses of valaciclovir, significantly reduces fetal viral load and improves the prognosis of moderately symptomatic infected fetuses [23]. This study, however, presents the use of a historical control group as a limitation, therefore...
requiring controlled randomized studies to confirm the results [23]. Given the higher probability of the NB to develop symptoms due to the potential NB immunosuppression caused by maternal chemotherapy and the best safety profile compared with other antivirals in pregnancy [24], the obstetric team decided to treat the fetal infection with valaciclovir. This decision is questionable since fetal treatment with valaciclovir was not yet validated and the encouraging results of the previously referred non-randomized study only concerns to moderately symptomatic fetuses, which was not the case.

Antiviral treatment in congenital CMV infection had also been the subject of controversy in the past, not only because of the risk of haematological toxicity, but also due to the lack of scientific evidence of its efficacy. Kimberlin demonstrated in a recent study with 96 NBs that treatment with valganciclovir in symptomatic infants, with or without CNS involvement, improves the auditory and neuro-developmental prognosis [25]. Therefore, antiviral treatment with ganciclovir or its oral pro-drug valganciclovir, may be useful in children with moderate to severe symptomatic congenital infection (disease with multiple manifestations or involvement of the CNS), and it should be initiated during the first month of life [24]. A better prognosis at 24 months was also verified in this study with ganciclovir/valganciclovir treatment for 6 months versus 6 weeks for hearing, language, and receiving communication [25]. There is currently no definitive evidence on the potential benefit of antiviral treatment in infants with mild symptomatic congenital infection or asymptomatic infants with isolated SNHL, and therefore is not recommended [24, 25]. One non-randomized single-blind clinical trial is investigating whether early treatment with oral valganciclovir of infants up to 12 weeks of age with congenital CMV infection and SNHL can prevent progression of hearing loss [26]. However these studies do not include extreme preterm infants and little is known about the efficiency, pharmacokinetics and safety of antiviral drugs in these NBs, which makes therapeutic decisions even more difficult. In this case report, towards a NB with CMV confirmed congenital symptomatic infection, with multiple severe manifestations and involvement of the CNS, treatment was started with ganciclovir on the 1st day of life. Although the initial decision was a 6-week treatment, at the time of relapse it was decided to undergo to an extended valganciclovir treatment for 6 months with an apparent positive short-term prognosis. This decision was made taking into account that there was a CMV infection recurrence after conventional treatment failure and the better results with oral valganciclovir treatment for 6 months versus 6 weeks reported in Kimberlin study [25]. However, this decision is controversial since this study only included babies with ≥ 32 weeks of gestation that initiated treatment during the 1st month of life, which did not happen in this case.

Ganciclovir has important side effects. Neutropenia is the most common side effect, occurring in about 65% of NB treated with this drug [1]. Thrombocytopenia occurs in 6% of cases [27]. Despite the reduction in the dose of ganciclovir chosen in this case when cytopenias developed, this procedure is controversial as it may promote the development of resistances.

Extreme prematurity and very low birth weight (VLBW) also constitute risk factors for SNHL with SNHL rates in this children group of about 5% [28-30]. Congenital CMV infection happens rarely in VLBW infants and it is associated with high rates of SNHL and neurodevelopmental impairment [31]. When this association occurs, like in this case, the SNHL rates can reach around 83% [31].

The authors intend to highlight the challenges of treating this infection, with a high morbimortality associated, since there are no definitive evidences about the potential benefit of fetal infection treatment during pregnancy, the evidences about the effectiveness of antiviral therapy in NB refer to a very restricted group of NBs and this therapy may be associated with important side effects. The existence of other factors that increase the NB vulnerability and potential sequelae make decisions even more difficult.

This case report cannot be considered as a paradigm as some of the therapeutic decisions are controversial and questionable. In the reported case the infant had many peculiarities that made him different from those enrolled in the available clinical trials, therefore the authors were forced to make difficult decisions in a field where there are not scientific evidences to support them.

Declaration of interest

The Authors declare that there is no conflict of interest.
References


