LUMEN ET VIRTUS

Congenital cytomegalovirus disease due to probable maternal reactivation: A case report

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ABSTRACT

Cytomegalovirus (CMV) is a member of the herpes virus family that is widely spread in humans and characterized by its ability to infect and reactivate after a latency period. Infection occurs through contact with infected body fluids, and therefore, pregnancy is an important period for alert and control. Congenital infection is more common and more severe, and presents symptoms ranging from jaundice to neural lesions. Thus, the aim of this study is to report a case of cytomegalovirus disease due to probable maternal reactivation. The case occurred in the municipality of Goiânia, in a pregnant woman attended at a private clinic in the municipality. Although maternal serology showed immunity to CMV, the patient had a systematic increase in bilirubin and jaundice. In neonatal serology, IgG was reactive and IgM was non-reactive, and no neurosensory involvements, cranial or abdominal alterations were observed. However, PCR indicated CMV infection and the patient continued with oral drug treatment and outpatient follow-up. The diagnosis of infection by maternal reactivation was based on the rapid appearance of the first symptoms of the disease. There is a

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greater need for discussions on the diagnosis and treatment of CMV by maternal reactivation, and more studies on the subject are important to guide medical practice.

Keywords: Vertical Transmission of Infectious Diseases, Cytomegalovirus infections, Neonatal Jaundice, Pediatric patient.

INTRODUCTION

Cytomegalovirus (CMV) is a virus of the Herpesviridae family, which together with Epstein-Barr (EBV); herpes simplex virus (HSV); varicella-zoster virus (VZV) and human herpesvirus (HHV), has all the properties of viral action, with double-stranded DNA, a capsid and a viral envelope. It is a virus widely spread among humans, whose virology confers characteristics of infection followed by a latency period and reactivation capacity (CARVALHO, 1999; NADEO; PASSOS-CASTILHO; GRANATO, 2015; PLOTOGEA et al., 2022).

CMV infection has endemic characteristics, with absence of seasonality, and a strong association with socioeconomic factors and age. Despite the scarcity of recent data on the prevalence of this infection, it is estimated that 40% to 80% of the world's population, 80% to 100% of Latin America, and 53% of the Brazilian population is infected with the virus (SANTOS, 2017).

The literature states that contact with CMV is cosmopolitan, and its transmission occurs through interpersonal exchange of infected body fluids, such as saliva, blood, urine, or genital secretions. Another type of infection occurs during or after childbirth, in the form of "cytomegalic inclusion disease" or congenital (intrauterine), and perinatal (birth). In general, congenital infection occurs transplacentally, while perinatal infection is associated with contact with cervical secretion in the birth canal, breast milk, or blood transfusion in CMV-seropositive individuals (LIRA et al., 2006; OLIVEIRA et al., 2011).

It is the most common cause of congenital infections worldwide (0.2 to 2.2%), and can be symptomatic or asymptomatic at birth. Even in its asymptomatic or mild form, it is a risk for newborns in immunosuppressed children, with clinical manifestations that can be severe, especially for the fetus (DEMMLER-HARRISON, 2009; EBRAHIMI-RAD et al., 2017; CRISMATT et al., 2020).

The prevalence of congenital CMV infection varies substantially in developing countries, with values between 6 and 14%. Between 85 and 90% of cases are asymptomatic, but 90% of symptomatic cases are severe, with a significant impact on quality of life and death. Among symptomatic cases, it is estimated that 5 to 15% of children may present late symptoms and develop progressive neural complications (MARIN et al., 2016; EBRAHIMI-RAD et al., 2017).

The prognosis and design of the follow-up of the disease is strongly influenced by the ability to differentiate between congenital and perinatal infection. In addition to being more frequent,

congenital infection is more severe, with a risk of sensorineural hearing loss, abnormalities in neurological development in newborns (NB) (OLIVEIRA et al., 2011; CRISMATT et al., 2020; PLOTOGEA et al., 2022). In general, the clinical manifestations most frequently found in the literature are petechiae, jaundice, and hepatomegaly, while neurological signs are nonspecific, and may present microcephaly, retinopathy, hypotonia with drowsiness, lethargy, difficulty sucking, and even seizures (CRISMATT et al., 2020).

It is known that maternal primary infection in the gestational period is associated with a higher risk of transmission and greater fetal impairment, however, congenital infections resulting from reactivation can present sequelae such as sensorineural deafness and loss of visual acuity (YIONON et al., 2010; OLIVEIRA et al., 2011). In this sense, the present study seeks to report a case of maternal congenital infection due to CMV reactivation and to discuss possibilities of diagnosis, treatment and conducts aiming at the best prognosis for the NB.

CASE REPORT

The information presented here was authorized by the patient's guardians through a Free and Informed Consent Form, and the project was submitted to the Ethics Committee of the Dona Iris Women's Hospital and Maternity Hospital, in Goiânia, Goiás, Brazil. This report is in accordance with the rules of Resolution 466/12 of the National Health Council on research involving human beings, and, as it is a completed case report, those responsible also signed a term of commitment and confidentiality, ensuring that personal data is not disclosed, and information used only for academic purposes.

JMF, 33 years old, G1P0A0, O+ blood type, started prenatal care in December 2021, IgG reagent and IgM not reactive for Cytomegalovirus (CMV), and dispensed new serology by the obstetrician. Endovaginal ultrasound (US) showed a single, viable topical pregnancy of 12 weeks and 2 days, and later, morphological ultrasound classified as normal, biometry and fetal biometric relationships normal, absence of echographic markers of chromosomal diseases, fetal echocardiogram showed normal fetal heart. In general, prenatal care indicated a pregnancy in the expected patterns for pregnant women and fetuses.

M.V.F, female, full-term RN, born on July 24, 2022; Weight: 2788g; height: 48 cm; head circumference: 34 cm; Apgar 8/9; blood type: O+, jaundice ++/V in Kramer. In the investigation of liver function, Total Bilirubin (BT) was identified: 6.4 mg/dL; Direct Bilirubin (BD): 0.2 mg/dL and Indirect Bilirubin (BI): 6.2 mg/dL, without jaundice at the level of phototherapy and medical discharge on July 26, 2022.

On the 7th day of life, the patient returns for medical care with BT: 16.3 mg/dL; BI: 15.6 mg/dL, and BD: 0.7 mg/dL, diagnosed with physiological jaundice followed by referral for

phototherapy. On the 8th day, BD was identified: 1.33 mg/dL; TGO: 65 U/L (VR: < or equal to 40 U/L)/ TGP: 47 U/L (VR: < or equal to 41 U/L); Hemoglobin (Hb): 7.5 g/dL; Hematocrit (Ht): 52.3 g/Dl. Gastropediatric evaluation, serology collection, and abdominal ultrasound for the next day were requested to investigate suspected cholestasis.

Abdominal ultrasound showed normal results, ruling out the diagnosis of cholestasis. The results of new tests showed BT: 9.02 mg/dL; BD: 0.47 mg/dL and BI: 8.55 mg/dL, non-reactive IgG and IgM for Herpes, EBV, Toxoplasmosis and Rubella, and CMV non-reactive IgM and reactive IgG were identified. The PCR for CMV in plasma was 62 IU/mL, however, the result was released 10 days after the test was performed (August 12, 2022).

On August 9, 2022, it was noted that phototherapy did not improve the condition and new tests were performed that showed a new increase in bilirubin (BT: 17.05 mg/dL, BD: 1.43 mg/dL, BI: 15.62 mg/dL), TGO: 84 U/L (RV: < or equal to 33 U/L), GT RANGE: 82 U/L (RV: <38 U/L), HBsAG: non-reactive, anti-HBc IgG/IgM non-reactive and VDRL non-reactive.

Hepatitis was suspected and serology was requested again, before the release of PCR for CMV. Thus, the investigation continued and on August 12, 2022, the PCR was released, and only on August 22 was the presence of CMV infection analyzed and identified and confirmation of the diagnosis.

After the diagnosis, imaging, ophthalmological, auditory and neural functions were performed. Total abdomen US was normal. In the ophthalmologic evaluation, structures of the anterior and posterior segments of the eyes were identified without abnormality; On fundus examination, the optic nerve was stained and flat, macular brightness was present, vessels were unaltered, vitreous was transparent, and the retina was free of lesions in both eyes. Otoacoustic emissions were present bilaterally, *and normal Transfontanellar Ultrasonography (*TFUS) and Brainstem Auditory Evoked Potential Examination (BERA) presented normal results. Audiological follow-up was suggested.

Due to CMV hepatitis, the pediatric infectious disease physician chose to start treatment with Valganciclovir (*Valcyte*®), although the ophthalmological, TFUS, and hearing exams were normal. Treatment was indicated for 6 months, orally, and use of 32 mg/kg/day. After initiating treatment with Valganciclovir (*Valcyte*®), laboratory follow-up was performed, the results of which are described below:

- First week of treatment (08/23/22 to 08/30/22): ANA: Non-Reactive; SMOOTH ANTI-MUSC AC: Non-reactive; ANTI-LKM1: Non-reactive; BT: 4.8 mg/dL, BD: 0.7 mg/dL, BI: 4.1 mg/dL. No alteration of renal function. TGO:55 U/L; TGP:30 U/L; GT RANGE: 82 U/L
- Segunda semana de tratamento (09/09/22): BT: 2,5 mg/dL, BD: 0,6 mg/dL, BI: 1,9 mg/dL,; TGO: 58 U/L, TGP:33 U/L

- Third week of treatment (09/17/22): BT: 2.1 mg/dL, BD: 0.6 mg/dL, BI: 1.5 mg/dL; AST: 51 U/L, TGP: 34 U/L, Hb: 9.4 g/dL identification of anemia by use of medication.
- Quarta semana de tratamento (25/10/22): BT: 0,48 mg/dL, BD: 0,17 mg/dL, BI: 0,31 mg/dL; TGO: 61 U/L, TGP: 48 U/L, Hb: 10,6 g/dL, Ht: 31,5 g/dL. PCR por CMV: Não detectado.

The NB is still under outpatient follow-up with evaluation of blood count, renal and hepatic functions due to possible complications due to the use of the medication. The diagnosis of congenital CMV due to probable maternal reactivation was justified by the speed with which symptoms and laboratory alterations were installed in the neonatal period.

DISCUSSION

Cytomegalovirus (CMV) infection is an important cause of recognized syndromes of fever, hepatitis, pneumonitis, encephalitis, and retinitis in infants. Symptomatic patients have a poor prognosis and asymptomatic patients have a risk of between 5-15% of having late manifestations, and 50% of sensorineural deafness. Attention to possible signs and symptoms of the disease is necessary for the accurate elaboration of a rapid diagnosis, as well as the correct identification of the form of infection. This is because the distinction between congenital and perinatal infection has great value in the prognosis and in the planning of the follow-up of these patients (PLOTOGEA et al., 2022; PEDRO et al., 2019; PAES, CIARLINI, 2015).

In the case in question, the maternal serology for CMV indicated that the mother had already had contact with the virus, but was not exposed at that time. Throughout pregnancy, obstetric imaging tests did not show intrauterine malformation or fetal growth restriction that would make the condition suspect. Ishi, Simões, and Alves (2021) state that maternal IgM and IgG serology, in 90% of cases, may be an indication of false positive and may be related to infection by another virus or autoimmune disease, however, it is characteristic of a probable recent CMV infection. They indicate that, even with positive IgM, it is important to perform the avidity test to define the period of infection, since IgM antibodies can disappear between 30 and 60 days, persisting for up to 10 months in ELISA. The recommendation is to repeat the serology in two weeks, because if it is CMV, the IgG will react (ISHI; SIMÕES and ALVES, 2021).

For some authors, the performance of these tests, in addition to being ineffective, is a common cause of problems among the health team and family members. This is because, for seronegative pregnant women, there are no methods of protection against infection other than the hygiene measures already taken, regardless of maternal serology or infectious agent, and for seropositive mothers, the possibility of fetal infection would only serve as an alert for the development of the disease, which is sometimes asymptomatic (BRASIL, 2015).

Thus, CMV screening is not a universal recommendation, however in Brazil, and more specifically in Goiás, maternal serology for CMV is included in the prenatal routine. It is known that clinical examination/diagnosis is not sufficient to detect active disease, since maternal symptoms are mild, nonspecific and can be confused with other diseases, and therefore, laboratory tests are decisive in the diagnosis of CMV infection by pregnant women (PEDRO et al., 2019; PAES, CIARLINI, 2015; OLIVEIRA et al., 2011).

During the neonatal period, a condition of jaundice was identified, initially treated as physiological, with good initial responses to phototherapy. It is a benign condition, common in newborns (30-60%), which is caused by the low capacity of the infant to eliminate bilirubin without any alteration in the metabolism of this molecule (COSTA; FRIEDRICH, 2010). Neonatal jaundice should always be investigated due to the potential for bilirubin toxicity at high concentrations and the risks of neurological changes due to this increase (ABOLURIN et al., 2020).

As the days progressed, there was a picture of increases in bilirubin values, including direct bilirubin, and the need for new tests emerged. Abdominal ultrasound was normal, eliminating the diagnosis of neonatal cholestasis, and serological tests of the main congenital infections showed no alterations, even for CMV.

In cases of CMV infection, it is recommended to perform Serology (IgM and IgG), PCR (polymerase chain reaction) and viral isolation in human fibroblast culture. PCR for viral DNA identification is recognized as a fast and efficient method, with the same efficacy as viral isolation, with the advantage of results in less than 24 hours and the possibility of storing samples (PAES, CIARLINI, 2015).

In the elaboration of the diagnosis, it is important to emphasize that, although the detection of the virus is direct and objective, it is possible to have situations with no association between serology, CRP and symptoms of the disease. In these cases, tests with quantification of viruses in the blood (e.g., quantitative plasma PCR) are increasingly available, and are useful measures to direct therapy, as well as provide prognostic guides for the outcome of congenital CMV infection in pregnancy (RAWLINSON, 2018).

It is important to note that under diagnostic conditions, it should be necessary to wait at least six weeks after the presumed maternal infection to confirm or exclude maternal-fetal transmission of CMV. There is a recommendation for the use of human immunoglobulin (HIG) as an approach to prevent or minimize vertical transmission of CMV infection or even minimize the effects that the disease may cause in RN (RYBAK-KRZYSZKOWSKA, 2023)

After the detection of CMV in CPA, the first attitude was to evolve to therapy. It is recommended that after diagnosis, clinical evaluation and complementary tests be carried out. Among the clinical examinations are the measurement of weight, length and head circumference, the

identification of hepatimetry and size of the spleen. Examinations of functions commonly affected by CMV are also important, namely: ocular fundoscopy, otoacoustic emissions, evoked potential of hearing (ABB) at birth, with follow-up of 3, 6, 12, 18, 24, 30 and 36 months, and cranial computed tomography. The suggested complementary tests are a complete blood count with platelet count, total bilirubin and fractions, serum transaminases, and, when possible, a cerebrospinal fluid test (RAWLINSON, 2018; BRAZIL, 2015; PAES, CIARLINI, 2015; ROSS; BOPPANA, 2005).

The literature presents some inclusion criteria for treatment, including: symptomatic NB, NB with evidence of sensorineural impairments such as intracranial calcifications, microcephaly, cortical atrophy, sensorineural deafness, abnormal cerebrospinal fluid and chorioretinitis; viral sepsis-like syndrome and CMV interstitial pneumonitis, under the age of 1 month (RAWLINSON, 2018; BRAZIL, 2015; PAES, CIARLINI, 2015; ROSS; BOPPANA, 2005).

The patient in question would meet the inclusion criteria in view of the progressive increase in bilirubin and age less than 1 month (28 days when I start treatment). At the request of the family, oral treatment with valganciclovir was chosen for 6 months, instead of intravenous ganciclovir for 42 days. It is a recommended antiviral and widely used in the pre- and neonatal period due to its good oral absorption, since it is available in liquid tablets, has few side effects and has a good concentration in the amniotic fluid (TESSIER, 2012).

Ganciclovir is also a frequently used drug, as it is well tolerated in newborns, has good CNS responses, and is not teratogenic. It also has benefits for neurological disorders and serious infections, however, it has already presented a risk of toxicity to the bone marrow. A dose of 8 to 12 mg/kg/day, every 12/12 hours, rediluted in 0.9% saline solution or 5% glucose solution, not exceeding 10 mg/ml, in a slow intravenous infusion for 1 hour, for six weeks (BRASIL, 2015; TESSIER, 2012; ROSS; BOPPANA, 2005).

All measures taken in the case followed the recommendations found in classical and recent literature. However, Tessier (2012) reinforces that the treatment of CMV infection or recurrence is a delicate topic, since the choice of drug, dose, duration, timing of treatment, and protocol of antiviral treatment are not yet "clearly codified". Thus, the first step in treatment is to determine whether the case is a primary infection or a relapse infection (TESSIER, 2012).

The hypothesis of infection by maternal reactivation, in this case, is based on the speed with which the symptoms and laboratory alterations were installed in the neonatal period, although few studies provide theoretical basis for this statement. A neonatal outcome of congenital CMV infection is influenced by several factors, including a Primary infection during pregnancy (risk between 30-50%) or infection within six months prior to conception (TESSIER, 2012; COSTA et al., 2021).

Vertical transmission can occur, even if less frequently (1.4%), since the virus has the ability to remain silently in different parts of the body, but mainly in salivary glands. Thus, there is the

feasibility of a viral reactivation of CMV from the impairment of the maternal immune system, causing a simultaneous viral or bacterial infection, or from a reinfection by new strains of CMV. In addition, laboratory studies have shown that pro-inflammatory cocktails were able to reactivate a CMV infection and consequently induce a primary infection (AZEVEDO et al., 2005; TESSIER, 2012; COSTA et al., 2021).

CONCLUSION

CMV infection continues to be an important cause of neonatal diseases in Brazil, and can cause sensorineural hearing loss, hepatitis, pneumotitis and death. Protocols and guidelines are widely found to guide screening and diagnosis aiming at maternal and fetal safety, as well as treatment, but little is discussed about cases of infection by reactivation.

The present report warns of the need to increase the frequency of CMV monitoring in prenatal care, differing from studies that indicate their inefficiency. The inconsistencies in monitoring are due to the fact that the serology performed does not indicate a risk of infection. However, in this study, the signs of the disease manifested in the first days of life and the diagnosis was concluded after confirmation of PCR. The treatment followed the guidelines available in the literature for congenital CMV infection and proved to be efficient.

The diagnosis of congenital CMV infection by maternal reactivation is a challenge and it is suggested that clinical trials, narrative and systematic reviews on the subject be carried out in order to assist health professionals in the management of this rare but serious infection. It is hoped that the recording of this report will contribute to the literary collection on the subject and to the guidance of gynecologists and pediatricians in similar cases.

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