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Clinical manifestations and management of congenital cytomegalovirus infection: A systematic review

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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on Congenital Cytomegalovirus Infection, seeking to identify the main clinical manifestations, as well

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as the main methods used in the treatment of this pathology. Methodology: It is a systematic review focused on understanding the main aspects of Congenital Cytomegalovirus. The research was guided by the question: "What are the main signs and symptoms of congenital Cytomegalovirus infection in the pediatric population, as well as what are the therapeutic resources used in clinical practice?". To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND". This resulted in 194 articles. 23 articles were selected for analysis. Results: Sequelae of congenital cytomegalovirus (cCMV) can occur in primary and non-primary maternal infections, and primary infections present a higher risk of transplacental transmission. Prenatal and neonatal screening is not routinely recommended due to the absence of preventive medication and difficulty in predicting sequelae. Sensorineural hearing loss is the most common sequelae, occurring in both symptomatic and asymptomatic cases. Antiviral treatments are promising but carry significant risks, and vaccination remains a developing challenge. Conclusion: Congenital CMV infections affect child development. Diagnostic advances, such as PCR, improve detection, but the lack of a vaccine and the need for preventive education are challenges. Antiviral treatment is effective, but requires close monitoring, so a multidisciplinary approach is essential to mitigate the impacts of congenital CMV and improve children's quality of life.

Keywords: Congenital Cytomegalovirus, Clinical Picture, Pediatrics.

INTRODUCTION

Cytomegalovirus (CMV) is one of the leading causes of congenital infections worldwide, occurring in 0.2% to 6.1% of live births. In South America, Africa, and Asia, cCMV rates tend to be higher, approximately 10–20 per 1,000 live births. (FOWLER. et al; 2018). CMV belongs to the human herpesvirus family and is the predominant virus in congenital infections. This condition represents a challenge for public health, affecting about 0.67% of live births. CMV can manifest as primary infection (PI) or non-primary infection (NPI), which occurs when there is later reactivation or reinfection. The estimated prevalence of cCMV at birth is three times higher in low- and middle-income countries compared to high-income countries. In addition, higher maternal CMV seroprevalence, higher population-level HIV prevalence, and young maternal age are associated with cCMV rates.(SSENTONGO. et al; 2021) (GANA. et al; 2024) (PINNINTI. et al; 2023)

This is a virus that exclusively affects humans and has a complex cycle. It can colonize the organism through community exposure (usually contact with young children) or blood transmission. When primary infection (PI) occurs, CMV goes through a replication phase and then spreads through the blood. Subsequently, it enters a latency phase, remaining inactive until some immunocompromised condition or triggering factor causes its reactivation. When there is reactivation or even reinfection with a new viral strain, we call this non-primary infection (NPI). During pregnancy, the primary infection is usually asymptomatic in about 90% of women. However, in some cases, it can manifest itself in a similar way to mononucleosis, with mild symptoms such as fever, rhinitis, pharyngitis, myalgia, fatigue, and dermatological manifestations. Laboratory findings such as abnormal liver function tests, atypical lymphocytosis, and hemolytic anemia may indicate the

need for immediate investigation for CMV. Conversely, non-primary infection usually does not cause maternal symptoms unless there is some degree of immunocompromise. (PINNINTI. et al; 2023)

CMV can be transmitted vertically from mother to fetus during pregnancy. The risk of transmission increases as pregnancy progresses. Transmission occurs more often after a maternal primary infection (PIM), with a risk of about 30-40%, than after a non-primary infection (NPI), with a risk of 1-2%. Although IPN is associated with a lower risk of transmission, it occurs more frequently due to the high worldwide prevalence of CMV (about 80%). CMV has an affinity for several cell types, including epithelial cells, endothelial cells, fibroblasts, and smooth muscle cells. Upon entry into the host, the virus establishes primary infection in organs such as the spleen, liver, and lungs. Viral spread occurs to other organs, such as salivary glands and kidneys, through infected epithelial cells and bodily secretions. (PINNINTI. et al; 2023) (KRSTANOVIC. et al; 2021)

CMV uses three main glycoprotein complexes (gB, gM/gN, and gH/gL) to enter cells. These complexes act sequentially: gM/gN makes the initial binding to host cells, gH/gL binds to cell surface receptors, and gB promotes membrane fusion. CMV encodes two types of gH/gL complexes: trimeric (gH/gL/gO), essential for infecting all cells, especially fibroblasts, and pentameric (gH/gL with glycoproteins UL128, UL130, and UL131), which is necessary for infecting epithelial cells, endothelial cells, leukocytes, and dendritic cells, but not fibroblasts. The ability of CMV to infect different cell types is related to the efficient exploration of multiple receptors and co-receptors on the surface of host cells. (KRSTANOVIC. et al; 2021)

Transmission of cytomegalovirus (CMV) from fetus-positive mothers begins at the uterus-placental junction, initially infecting the uterine smooth muscles and endothelial cells in the decidua. Then, the virus's interactions with trophoblastic cell receptors allow transplacental transmission, carrying the virus into the fetal blood system. CMV is thought to enter the fetal circulation in a cell-free form, due to the limited permeability of the placenta. Once in the fetal blood system, CMV replicates in multiple fetal organs, although the exact route of spread from the placenta to individual organs, including the brain, is not yet completely understood. However, CMV is known to have an affinity for central nervous system and inner ear cells, which contributes to the clinical presentation of infection, including brain abnormalities, hearing loss, seizure, microcephaly, and intrauterine growth restriction. (KRSTANOVIC. et al; 2021) (PESCH. et al; 2021)

Congenital cytomegalovirus is a leading cause of sensorineural hearing loss (SNAP) and neurodevelopmental delay in children. The majority of congenitally infected infants (~90%) do not have any obvious clinical abnormalities at birth and are therefore asymptomatic. Infants with symptomatic infection are those who have clinical findings at birth suggestive of congenital infection. There are important prognostic implications associated with this categorization, because

infants with symptomatic infection are more likely to have neurodevelopmental sequelae and SNAP. (FOWLER. et al; 2018)

This systematic review article aims to compile and analyze the scientific evidence on the clinical manifestations and management of congenital cytomegalovirus infection. The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis of the evidence is intended to be a useful resource for health professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches to this pathology.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of the clinical manifestations of Congenital Cytomegalovirus in pediatric patients, as well as to demonstrate the main methods used in the treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main signs and symptoms of congenital Cytomegalovirus infection in the pediatric population, as well as what are the therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term "AND": Cytomegalovirus Infections, Signs and Symptoms, Pediatrics and Newborn. The search strategy used in the PMC database was: Cytomegalovirus Infections AND newborn; Cytomegalovirus Infections AND Signs and Symptoms e Cytomegalovirus Infections AND Pediatrics. From this search, 194 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 194 articles were found. After applying the inclusion and exclusion criteria, 34 articles were selected from the PubMed database, and a total of 23 studies were used to compose the collection.

DISCUSSION

Sequelae associated with congenital CMV (cCMV) can arise in both primary and non-primary maternal HCMV infections. Primary maternal HCMV infections are characterized by

acquisition of HCMV during pregnancy in a person without pre-existing HCMV-specific IgG antibodies. Non-primary maternal HCMV infections are defined as active HCMV infections in pregnant women with pre-existing HCMV-IgG antibodies. Although most of the burden attributable to cCMV is due to non-primary HCMV infections, the risk of transplacental transmission of HCMV is higher with primary infections, ranging from 21% in the periconceptional period to more than 50% in the third trimester, although with lower severity. (PINNINTI. et al; 2023)

Transmission of cytomegalovirus (CMV) through breast milk in premature infants is likely to occur transmucosally. It is still unclear exactly where this transmission occurs anatomically. Preterm infants often receive enteral feeding via gastric or jejunal feeding, which suggests that breast milk-associated CMV infection may be transmitted at the mucosal level of the small intestine. Studies also indicate that CMV infection can begin in the oropharyngeal or nasopharyngeal epithelium, with subsequent spread to regional lymph nodes and generalized end-organ infection. Regardless of the route of entry of the virus, not all babies exposed to CMV-positive breast milk are infected. Studies investigate whether babies who acquire the infection have specific deficits in adaptive immunity. Transmission of cytomegalovirus (CMV) through breast milk is an important issue. Studies have examined the relationship between CMV-specific antibody levels in breast milk and transmission to preterm infants. Although there is no clear correlation between antibody titers and transmission, lactoferrin in breast milk may also play a role in protecting against infection. However, it is not yet clear whether maternal antibody benefit occurs in the mucosal or systemic compartment. More research is needed to fully understand these mechanisms and their effects on long-term neurological development. (OSTERHOLM. et al; 2020)

As one of the leading causes of congenital infections worldwide, cCMV infection meets many of the screening criteria: it is clinically important, well-defined, and prevalent. However, neither universal prenatal screening for CMV during pregnancy nor universal neonatal screening is routinely recommended. Reasons for not screening include the absence of medication to prevent transmission and the difficulty of predicting sequelae. (LAZZAROTTO. et al; 2020)

Congenital cytomegalovirus (cCMV) is a common infection in newborns and the leading cause of non-genetic hearing loss. Screening for cCMV is important, as most infected children are asymptomatic at birth. Early diagnosis allows for appropriate interventions. Studies support the importance of identifying the preclinical phase to avoid delays in intervention. Currently, there is research on the use of antiviral therapy to improve auditory outcomes in infants with asymptomatic cCMV. (HALLER. et al; 2020)

There are several suitable tests for the diagnosis of congenital cytomegalovirus (cCMV). Screening can be carried out through saliva or urine tests, detecting the virus's DNA by PCR or culture, before the baby is 3 weeks old. However, it is important to note that subsequent tests cannot

differentiate congenital infection from postnatal infection, which does not cause sensorineural hearing loss (SNAP). Saliva collection is simpler, but it can present false-positive results, possibly due to breast milk. It is recommended to wait at least 90 minutes after breastfeeding to obtain a saliva sample and a confirmatory urine sample in infants with a positive saliva result. In addition, studies are underway to compare the analytical sensitivity of CMV PCR in saliva with PCR from neonatal dried blood (DBS) samples. (HALLER. et al; 2020)

The introduction of routine testing for CMV in pregnant women has several implications. Despite the difficulties mentioned above, the most important benefit of screening would be to identify fetuses at risk of developing sequelae. Maternal screening, ideally early in the first trimester, would also identify those who were CMV seronegative and thus allow for the provision of information on hygiene and behavioral measures to prevent CMV infection. Evidence shows that intervention based on identification and hygiene counseling of CMV-seronegative pregnant women significantly prevents maternal infection.(LAZZAROTTO. et al; 2020)

Serology is also indicated in pregnant women with symptoms compatible with primary CMV infection, such as moderate prolonged fever, mononucleosis syndrome, or elevated liver transaminases. CMV serology may also be performed when abnormal sonographic features suggest fetal infection. In these cases, a negative serology excludes fetal infection and a serology with positive IgG, regardless of the IgM or IgG avidity value, cannot exclude fetal infection.(LERUEZ-VILLE. et al; 2024)

During early pregnancy, repeat serologic screening with CMV-specific immunoglobulin G (IgG) and -M (IgM) antibodies from previously seronegative pregnant women at the end of the first trimester (or up to week 20) would identify primary maternal CMV infection. Although there are no universally accepted guidelines, testing before 18-20 weeks of pregnancy is reasonable to identify late seroconversion at the end of the first trimester and implement fetal investigations. In case of seroconversion, parents should be informed of the risk of vertical transmission and the possible consequences. (LAZZAROTTO. et al; 2020)

During pregnancy, IgG and IgM serology is the preferred option; IgG avidity testing should be used only if CMV-specific IgM antibodies are positive. Many laboratories consider positive results for IgM, in combination with IgG avidity results, to discriminate between primary and non-primary CMV infections. IgG avidity, which measures the binding strength of CMV to IgG antibodies, is an indicator of antibody maturity and can be useful in assessing the timeliness of an infection. A lower IgG avidity indicates less mature antibodies and is suggestive of a more acute infection. The Society for Maternal-Fetal Medicine recommends that a person with suspected primary CMV infection during pregnancy be tested and diagnosed by IgG seroconversion or by a

CMV-positive IgM, positive IgG, and low IgG avidity.(LAZZAROTTO. et al; 2020) (PESCH. et al; 2021)

The history of CMV vaccines began with preparations based on live attenuated viruses in the 1970s. However, the effectiveness of these vaccines was limited. Currently, research continues to develop a live attenuated vaccine, and approaches with specific proteins (such as gB, the pentameric complex, and pp65) have shown promising results. The duration of protection offered by the different vaccines is not yet fully defined, and strategies range from universal immunization to the selection of HIV-negative women before vaccination. In addition, the economic importance of vaccination remains under debate. In summary, although challenges persist, progress continues in the search for an effective solution against CMV. (ESPOSITO. et al; 2021)

To date, no vaccine is licensed for the primary prevention of CMV infection, but a phase 3, randomized, placebo-controlled trial is currently underway evaluating the efficacy, safety, and reactogenicity of an mRNA-CMV vaccine in non-pregnant HIV-negative women. An alternative strategy to reduce the risk of infection is behavioral recommendations that minimize direct contact with biological fluids from young children. Several studies have reported that not only women but also healthcare professionals have inadequate knowledge about preventive measures for cCMV, so education about preventive strategies should be a mandatory part of prenatal clinical counseling. The main recommendations should focus on hygiene measures, such as washing hands in case of contact with children's saliva or urine or avoiding intimate contact, such as kissing and sharing utensils. Several trials have provided evidence that the rate of seroconversion was significantly reduced using these preventive measures, which are widely accepted among pregnant women, which demonstrated the ability to sustain behavioural changes, feeling that these recommendations are worth suggesting and not worrying about limiting intimate contact with their children (PINNINTI. et al; 2023)

A systematic review and meta-analysis investigated antenatal therapy with valacyclovir after maternal cytomegalovirus (CMV) infection. The results indicated that the use of valacyclovir reduces the risk of congenital CMV infection and increases the likelihood of asymptomatic infection. However, there was no conclusive evidence that treatment with valacyclovir improved the prognosis of fetuses after established congenital infection. In addition, the risk of serious adverse events in pregnant women who took valacyclovir was small and resolved after discontinuation of the medication. It is important to interpret these results with caution due to the small number of cases in the studies analyzed. Although symptomatic CMV infection is rare, more research is needed to fully understand the role of valacyclovir in the prevention and treatment of congenital CMV infection. In summary, antenatal therapy with valacyclovir appears to be promising in preventing mother-to-child transmission of CMV, especially when the infection is acquired in the first trimester of pregnancy.

However, screening recommendations and models to predict adverse outcomes in fetuses with congenital CMV infection still need to be further developed. (D' ANTONIO. et al; 2023)

According to (LANZIERI. et al; 2020), five mathematical models of cytomegalovirus (CMV) infection in the United States, the United Kingdom, and Brazil are presented. These models help to understand the dynamics of CMV transmission in populations with different levels of seroprevalence. They also evaluate the potential impact of vaccination on the prevention of congenital CMV infection and its complications. Overall, childhood vaccination (for both sexes) was found to be the optimal strategy to reduce congenital CMV infections in four of the models. In the fifth model, optimal strategies to prevent congenital disabilities associated with CMV included childhood vaccination with 4-year protection or vaccination of HIV-negative women between 19 and 21 years, with protection of at least 8 years. It is worth noting that while youth vaccination has a large predicted impact, reduced transmission combined with decreased natural immunity could increase the average age at which people acquire primary CMV infection, especially in populations where primary infection occurs in childhood, such as in Brazil. This phenomenon has already been observed in other diseases, such as congenital rubella syndrome, in countries with low vaccination coverage against rubella. The study also highlights that in Brazil, about 10% of congenital CMV infections result from primary maternal infection, as evidenced by a large Brazilian study, and 15% based on model estimates. Different vaccination strategies were evaluated, including childhood vaccination (both sexes) and vaccination of HIV-negative women at 19-21 years of age. The models suggest that childhood vaccination is the ideal strategy, but vaccinating young women can also be effective. The duration of vaccine protection and the variation in CMV seroprevalence among populations are important factors to consider. In addition, the frequency of reinfections and reactivations in populations with high CMV seroprevalence needs to be better understood to inform vaccination strategies. (LANZIERI. et al; 2020)

Approximately 10% of infants with cCMV will present with clinical anomalies at birth and will therefore be classified as symptomatic. There is no standard definition for symptomatic cCMV infection, as studies will include different clinical manifestations. In general, infants with symptomatic cCMV infection may exhibit a wide range of disease manifestations. Severely symptomatic infection may manifest as thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, and hepatitis. Central nervous system (CNS) involvement by cCMV manifests as microcephaly, neuroimaging abnormalities such as ventriculomegaly, intracerebral calcifications, periventricular echogenicity, and seizures. Ophthalmologic examination may reveal chorioretinitis or optic atrophy. Mortality due to cCMV is generally low, with approximately 4% of infants dying as a result of cCMV. (FOWLER. et al; 2018)

Among children with symptomatic cCMV, 50–60% are at risk of developing long-term sequelae – sensorineural hearing loss (SNAP) is the most common, followed by developmental disabilities, chorioretinitis, and cerebral palsy. Hearing loss is the most frequent sequelae in both symptomatic and asymptomatic cMCV. Among children with symptomatic cCMV, 30%–40% will have SNAP in the neonatal period or in the first years of life. Late-onset hearing loss is common, as 18% to 27% of symptomatic infants develop hearing loss after birth. Progression of hearing loss over time occurs in 20% to 54% of symptomatic infants, and 43% of SNAP is bilateral and severe/profound. A hallmark of HCMV-related hearing loss is fluctuating hearing loss that can occur unilaterally or bilaterally. (PINNINTI. et al; 2023) (FOWLER. et al; 2018)

About half of infants with symptomatic cCMV infection will have permanent sequelae: mainly PASN, followed by cognitive deficits, chorioretinitis, and cerebral palsy. On the other hand, infants with asymptomatic cCMV infections rarely suffer from neurodevelopmental sequelae and show no difference in their intelligence quotient (IQ) compared to normal control infants. (GERNA. et al; 2021)

The symptomatic status is further differentiated into mild, moderate and severe states, based on the strong association of symptoms, although the most severe consequences of cCMVc infection – PASN and long-term neurological sequelae – can occur in both symptomatic and asymptomatic newborns. This postnatal classification has a good correlation with prenatal care, defining infected fetuses according to the presence and severity of symptoms: asymptomatic fetuses are those without USG, magnetic resonance imaging, and fetal blood abnormalities. Mild or moderate symptomatic fetuses are those with isolated biological anomalies, without brain lesions, or with isolated anomalies, such as hyperechoic bowel, mild ventriculomegaly, or isolated calcifications; Severe symptomatic fetuses are those with severe US anomalies, such as ventriculomegaly, intracerebral hemorrhage, associated with thrombocytopenia. (PINNINTI. et al; 2023)

A distinct category is that of asymptomatic patients infected with cCMV with isolated sensorineural hearing loss (PASN). This asymptomatic disease is defined by those with a normal physical examination. However, it is important to note that this categorization can be somewhat artificial, and researchers have reported that apparently asymptomatic babies may have laboratory or neuroimaging abnormalities. Late diagnosis of cCMV-induced PASN in asymptomatic infants may result in risks, such as speech, language, and learning delays. Therefore, addressing hearing loss as early as possible allows for appropriate interventions. An audience-directed screening (HT-CMV) approach has been implemented in some US states, linking it to universal newborn hearing screening. The decision to establish CMV-HT screening as a medical practice should consider the risks and benefits to patients, families, and society at large. The principles of tracking are defined by

established criteria, but successful implementation still requires careful consideration. (HALLER. et al; 2020)

Children with symptomatic cCMV had rates of global developmental delay ranging from 43% to 64%. Infants with symptomatic cCMV were more likely to develop late, especially those with microcephaly or small for gestational age at birth. In studies with asymptomatic children, there were no significant differences in overall developmental outcomes compared to uninfected controls. As for fine and gross motor skills, most studies found no differences between children with cCMV and controls. In addition, some studies have focused on children with symptomatic cCMV and reported language disorders. On the cognitive side, the results varied, but it is essential to monitor these children and provide appropriate clinical guidance. (PESCH. et al; 2024) Studies have evaluated outcomes in children with cCMV without symptoms at birth, indicating that, in general, children with AcCMV have better neurodevelopmental outcomes than those with symptomatic cCMV. (SMYRLI. et al; 2024)

Laboratory findings in infants with cCMVc infection will reflect the organ systems involved. As such, more than 50% of children with symptomatic infection may have conjugate hyperbilirubinemia, elevated liver transaminases, or thrombocytopenia. Bilirubin and transaminase levels will peak in the first 2 weeks of life, but may remain elevated for several weeks. Thrombocytopenia tends to reach its lowest point in the second week of life and will completely normalize within 3 to 5 weeks of life. (FOWLER. et al; 2018)

Treatment for congenital cytomegalovirus (cCMV) infection encompasses several options, including antiviral therapy, auditory amplification, cochlear implantation, speech therapy, and physical therapy. In the case of CMV-induced hearing loss, antiviral therapy has been studied, but the results are inconclusive. Some studies report improvement in hearing outcomes after administering antiviral therapy, but others question its effectiveness. These clinical trials are ongoing to evaluate the impact of the antiviral VGCV in symptomatic and asymptomatic children with PASN. Treatment with CVVV is not currently recommended for children with isolated SNAP, but participation in clinical trials is encouraged. (HALLER. et al; 2020)

CMV is a virus that affects both pregnant women and children. About 90% of children born to mothers with CMV infection develop an asymptomatic infection. However, cCMV represents a notable concern, and can cause sensorineural hearing loss (SNAP) and long-term neurological sequelae in infants, regardless of whether they are symptomatic or asymptomatic. The risk of vertical transmission of CMV increases with advancing pregnancy. Ultrasound (US) plays a crucial role in detecting anomalies associated with CMV during pregnancy, including placental, extracranial, and brain changes. Transvaginal US and targeted neurosonography are important to evaluate the fetal brain in detail. Although there is no licensed vaccine for primary prevention, behavioral strategies

such as avoiding direct contact with biological fluids from young children are recommended. Regular US follow-up is essential for fetuses with known or suspected CMV infection. (D'ALBERTI. et al; 2024)

Improved methods for cCMV detection have been developed and validated in recent years. The gold standard for identifying infants with cCMV has been the detection of viruses in saliva or urine samples obtained in the first 2–3 weeks of life, this is because after this period the detection of CMV may be due to a congenital infection or postnatal infections acquired by breast milk or transfusion. Therefore, to assess the natural history of cCMV infection, the relationship between cCMV infection and the presence of defects at birth or their appearance during childhood, it is essential to test biological samples collected in the first 15-21 days of life.(RAZONABLE. et al; 2020) (PELLEGRINELLI. et al; 2020)

The development of new methods for sample collection and application of high-throughput molecular methods, such as quantitative polymerase chain reaction (qPCR), has largely supplanted culture-based methods in most laboratories and is paving the way for the widespread implementation of newborn screening programs for cCMV internationally. PCR assays have the advantage of being cheaper, with fast turnaround times and no need for maintenance of tissue culture facilities. A DNA extraction step is not required for QNAT testing of saliva samples. PCR is also less affected by sample storage and transport conditions and can be adapted for use in high-throughput newborn screening programs. The sensitivities for PCR detection of HCMV DNA are similar with both types of samples, both saliva and urine, presenting a percentage of 99.7% agreement. (RAZONABLE. et al; 2020)

In a screening study for HCMV in newborns, qPCR assays of dry saliva and liquid saliva samples were compared with rapid saliva culture for the detection of HCMV in 34,989 newborns; qPCR methods had a sensitivity of 97.4% to 100% and a specificity of 99.9%. In a study conducted in Brazil, PCR tests of urine samples for detection of CMV DNA to diagnose cCMV demonstrated high sensitivities (ranging from 93% to 100%). (RAZONABLE. et al; 2020) (PINNINTI. et al; 2022)

One of the concerns about saliva testing to detect CMV-infected infants is the possibility of incorrect identification of HCMV infection in newborns due to the presence of HCMV in the mother's genital tract and breast milk. However, in the CHIMES study, the frequency of positive results for HCMV attributable to contamination of breast milk by saliva qPCR was less than 0.03%. The frequency remained low even when adjusted for national HCMV seroprevalence and breastfeeding rates, indicating that saliva PCR results are unlikely to be significantly influenced by breastfeeding.(RAZONABLE. et al; 2020)

Since 1988, antiviral drugs have been used in the treatment of cytomegalovirus (CMV). Studies show that newborns with symptomatic CMV, who have multiple CMV-related anomalies at

birth, have better long-term auditory and neurocognitive outcomes when treated with antiviral agents such as ganciclovir or valganciclovir. As physicians, our goal is to identify diagnoses in order to offer effective and curative treatments. However, in the case of asymptomatic congenital cytomegalovirus (cCMV), we do not yet have a proven treatment option. Currently, antivirals are being offered off-label to patients with asymptomatic cCMV, but these drugs carry significant risks. Short-term side effects include neutropenia, thrombocytopenia, hepatitis, and nephrotoxicity, requiring frequent and uncomfortable laboratory monitoring. In addition, the long-term side effects of these antiviral agents, documented in animal studies, include potential teratogenicity and gonadotoxicity. Doctors who prescribe these off-label antivirals also face moral and legal risks. Monitoring the therapeutic effect of these treatments in the asymptomatic cCMV population is challenging, since most patients will never develop sequelae, regardless of treatment. Therefore, determining treatment success in these asymptomatic patients is an arduous task with no measurable improvements or clear outcomes. (GIEVERS. et al; 2020)

Antiviral treatment with oral valganciclovir (VGCV) for 6 months compared to 6 weeks has been shown to be beneficial for hearing and neurodevelopmental outcomes in neonates with moderate to severe symptomatic cCMV if started in the first month of life and is considered standard of care. After oral ingestion, valganciclovir is rapidly converted to ganciclovir. When valganciclovir is administered at a dose of 16 mg/kg twice daily, the plasma concentration achieved is comparable to that of ganciclovir at a dose of 6 mg/kg. Valganciclovir leads to a temporary reduction in viral load, which reverts to its original level after stopping treatment. Prolonged use of the drug can lead to the emergence of resistant viral strains. Myelosuppression and liver damage are the expected side effects of VGCV, and close follow-up is recommended throughout the duration of treatment. Due to the lack of established efficacy, antiviral treatment is not currently recommended for children with asymptomatic cCMV or those with isolated PASN, pending data from ongoing studies. (PINNINTI. et al; 2022) (GANA. et al; 2024)

Regarding the treatment of congenital sensorineural hearing loss, universal screening of congenital hearing loss is recommended, as early diagnosis promotes early intervention to reduce irreversible damage to speech development. Treatment of congenital hearing loss depends on the underlying cause. When the cause is not known, an MRI should be performed to evaluate the anatomy of the inner ear. The first drug administered is oral corticosteroids. If no improvement is seen within 10 to 14 days, doctors use rescue intratympanic steroids. Hearing aids are used in chronic conditions. Surgical management is represented by cochlear implants in patients where hearing aids are not useful. (GANA. et al; 2024)

It is recommended that children with cCMV be followed up with serial audiological evaluations starting in the neonatal period, repeated at 6-month intervals during the first 3 years of

life, and annually thereafter until adolescence. With emerging evidence that vestibular dysfunction occurs frequently in children with symptomatic and asymptomatic cCMV and the association between PASN and vestibular dysfunction, it is likely that infected children will benefit from routine periodic vestibular evaluations, incorporated into neonatal hearing screening and audiological protocols. (PINNINTI. et al; 2022)

CONCLUSION

Congenital cytomegalovirus (CMV) infections represent a significant concern due to their potential consequences for child development. Although universal screening for CMV during pregnancy or neonatal care is not routinely recommended, early maternal and newborn screening can play a crucial role in identifying infections and implementing preventive measures. The introduction of routine testing can help identify fetuses and newborns at risk, allowing for timely interventions and reducing long-term sequelae.

Advances in diagnostic methods, such as PCR, have improved the early detection of CMV in newborns, enabling more effective treatments. However, the lack of a licensed vaccine and the need for broader education on preventive measures among pregnant women and healthcare providers highlight the importance of a comprehensive approach to the management of congenital CMV. Antiviral treatment, while beneficial for symptomatic infections, still presents challenges such as viral resistance and side effects, reinforcing the need for rigorous and continuous follow-up.

In summary, the multidisciplinary approach involving early screening, preventive education, diagnostic advances, and appropriate treatments is essential to mitigate the impacts of congenital CMV. Regular follow-up of infected children is essential to monitor and manage long-term complications, ensuring a better quality of life and healthy development.

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