An update on congenital CMV

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Abstract

Congenital cytomegalovirus (cCMV) infection is an important cause of lifelong sequelae such as neurodevelopmental impairment and sensorineural hearing loss (SNHL). Although many questions regarding this disease have been resolved, many topics are still under discussion. Counseling of (future) parents is therefore challenging.

This narrative review aims to give an overview on diagnosis, management, treatment and prevention of cCMV in pregnant women and their babies in order to help the clinician in counseling and making a decision for referral.

Introduction

Nowadays, when talking about "the virus" many people can only think of coronaviruses. However, with an incidence of 0.5-2% worldwide, being the main cause of non-genetic sensorineural hearing loss (SNHL) and an important cause of neurodevelopmental problems, congenital cytomegalovirus (cCMV) might be called "the virus" in perinatology.

CMV is a member of the family of *Herpesviridae*, which have the ability to stay latently present in the body after a primary infection. Transmission occurs through contact with infected bodily fluids (urine, saliva, vaginal secretion, semen, breastmilk) or blood-contact (transfusion or organ transplantation). The seroprevalence in women of childbearing age is around 50 % in developed countries and even higher in developing countries. In immunocompetent adults and children, CMV infection usually does not cause severe symptoms. However, when a CMV infection occurs during pregnancy, there is a risk of transferring the infection to the fetus. Such is possible in women without pre-existing immunity against CMV (primary infection), but also in women with antibodies from a previous CMV infection by reactivation of the virus or infection with a different strain of CMV (non-primary infection) (1).

Prenatal diagnosis

Routine antenatal screening for CMV is currently not recommended in pregnancy, which was also emphasized in a knowledge report of the Belgian Health Care Knowledge Centre (KCE) in 2015 (2). This is partly due to the fact that CMV does not meet some of the criteria for screening tests. However, the current lack of effective prenatal treatment also contributes to the current recommendation (1, 3). Women are tested in case of flu-like symptoms or if prenatal ultrasound is suggestive of cCMV infection (3). Possible signs on fetal ultrasound are intra-uterine growth retardation, fetal ascites, hydrops fetalis, oligohydramnios, microcephaly, intracerebral calcifications and echogenic bowel (1).

The gold standard for determining maternal primary CMV infection is serologic testing, with IgG and IgM being the preferred option (4). If CMV IgG is detected in combination with CMV IgM, it is important to determine the moment of infection. The CMV IgG avidity assay is considered a primary tool for this purpose. IgG avidity increases with time: infections with low-avidity IgG are considered recent infections (3-4 months), while a high avidity index is present in case of past infections (3). The presence of CMV IgM and low-avidity IgG is very effective in diagnosing primary CMV infection during pregnancy (4). Until now, there are no validated tools (serological or virological) to diagnose secondary CMV infections in a precise manner (1, 5). Maternal serology screening can be falsely reassuring as it will not always identify non-primary infections.

Once seroconversion is diagnosed, a thorough follow-up of the pregnancy is mandatory to identify the (seriously) affected children. Identifying which foetuses are affected, and to what extent, is challenging. Structural foetal ultrasound, amniocentesis for culture or PCR and prenatal MRI all have their role in diagnosing cCMV and predicting its outcome (4). The sensitivity of prenatal diagnosis techniques varies depending on the population selected, the gestational age at the time of the investigation and the gestational age at the time of infection (5).

Prenatal ultrasound can help detecting structural or growth abnormalities that may suggest foetal infection, but many of these findings are non-specific for CMV (intra-uterine growth retardation, echogenic bowel, ventriculomegaly, calcifications, hepatosplenomegaly) (1, 4).

Amniocentesis is commonly used to diagnose foetal infection. It must be performed after 21 weeks of gestation and at least 6 weeks after maternal infection (5). If CMV-DNA PCR on amniotic fluid is positive, the diagnosis of congenital CMV infection is confirmed (high specificity). However, a negative PCR on amniotic fluid does not rule out congenital CMV infection (low sensitivity). In order to exclude false-negative CMV PCR on amniotic fluid, confirmation of diagnosis by neonatal testing is essential, since neonatal testing has a much higher sensitivity. Hence, future parents must be counselled on the importance of neonatal testing and need to be aware of the fact that a positive result on amniocentesis does not provide any information on future cognitive development of the infant and severity of sequelae (4). Cordocentesis has the same sensitivity and specificity as amniocentesis but the risk of complications is higher, which makes amniocentesis the preferred diagnostic technique (5).

The use of prenatal MRI has increased over the last years. Prenatal cerebral MRI is a valuable tool adding information to fetal ultrasound if performed at the right time (> 32 weeks of gestation) and if interpreted by people who

are experienced in evaluation of foetal brain imaging (6, 7). Appropriate integration of foetal MRI into prenatal diagnostics can lead to a more accurate counselling and/or more appropriate management (6).

Prenatal management

Over the years, several prenatal therapeutic options have been studied, such as immunoglobulins and valaciclovir during pregnancy. No conclusive results have been published so far. Hence, since further studies on the different therapeutic options are still warranted, prevention of CMV infection plays a key role, e.g., vaccines and hygiene measures.

Valaciclovir during pregnancy

The question rises if prenatal treatment with valaciclovir could improve the prognosis of infants affected with cCMV. Recent research indeed shows a possible advantage of treatment with valaciclovir during pregnancy, especially if the treatment is given at an early stage of infection and in the first trimester (8). However, since the majority of CMV infections are subclinical, this would mean that early-pregnancy serologic screening should be performed on all pregnant women in order to identify the CMV infection early.

Valaciclovir during pregnancy is classified as a group B drug, which means there is no clear evidence of risk in humans. However, given the lack of large controlled safety studies on this topic, reliable and definitive conclusions cannot be drawn (9).

Immunoglobulins

Administration of hyperimmune globulin monotherapy before the 24th week of pregnancy did not show an amelioration in neonatal outcome (10). Currently, trials with a combination of valaciclovir and hyperimmune globulins show promising results (11).

Vaccines

The first attempt to develop a vaccine against CMV infection began in the 1970s. In 2000, the Institute of Medicine in the USA gave CMV vaccine the highest priority within the vaccine development program and stimulated the development of several vaccine candidates. The development of such a vaccine is complex, due to the nature of CMV protective immunity (antibodies and T-Cell responses) and the capacity of CMV to remain latent in the body. In order to prevent congenital infection, the vaccine should be able to protect both seronegative women from primary infection and seropositive women from reinfection and reactivation (12). Several CMV vaccine candidates are in different stages of development, of which the more promising ones appear to be able to express several antigens. The different strategies of vaccination have yet to be elucidated (pregnant women, universal vaccination of 12-year-old boys and girls, vaccination of seronegative women of child-bearing age).

Education of pregnant women

Although the various clinical trials on vaccines seem promising, none will be available immediately. Hygiene information and education of pregnant women is therefore currently the most effective strategy for prevention of CMV infection (13). CMV is transmitted by direct contact with bodily fluids (urine, saliva, etc.) and can remain on soiled surfaces for a few hours. Children, mainly under 6 years old (with a peak between 1 and 2 years old), are the main vectors of the disease. An effective strategy to reduce maternal CMV infection in future mothers is raising their awareness of the risk of cCMV and the existence of possible strategies to prevent such infection. Possible prevention consists of simple hygiene measures, especially in women who already have children or work with young children (14).

To aid this education, several media (video, brochures, etc.) are available: the CDC has published hygiene measures for pregnant women on its website, and in Belgium both the ONE (Office National de l'Enfance) and Kind en Gezin have published brochures in French, Dutch and English to educate women on the prevention of congenital CMV infection.

Postnatal Diagnosis of cCMV

Identification of infants with congenital CMV (cCMV) infection

At this point, no universal neonatal screening is performed. Hence, testing for CMV in neonates is only recommended in case of the presence of any sign indicative of intra-uterine CMV infection or after known maternal seroconversion.

Until recently viral isolation and culture from urine was the gold standard for diagnosing cCMV infection. Since PCR on urine has high sensitivity (100%) and specificity (99%) and the results are more rapidly obtained than cultures, this is now the preferred diagnostic technique. One urine sample is sufficient to confirm the diagnosis (3). CMV PCR testing of saliva is an alternative technique and easier to perform. Saliva samples should be taken immediately before feeding in breastfed newborns, and confirmed with urine, as false-positive results have been reported (18). A study by Exler et al. found that overall concordance of CMV DNA detection in neonatal saliva and urine is 91% and that PCR in saliva compared to urine, showed a positive predictive value of 73% (15). If available, screening with PCR on saliva and confirmation with PCR on urine is the least invasive, but most reliable method.

The PCR on urine can only be performed during the first 3 weeks of life. After this age, there is a possibility that a postnatal infection (e.g. through breastmilk) is detected. So, in case of diagnosis after 21 days, congenital CMV infection must be confirmed by detection of PCR CMV-DNA on the dried blood spot (neonatal screening card) (3, 16).

Diagnostic work-up in the newborn

As soon as congenital CMV is confirmed in the neonate, a thorough clinical examination and diagnostic work-up should be performed, consisting of laboratory testing, cranial imaging, hearing screening and ophthalmological evaluation. This will allow to identify the consequences of fetal infection and to classify the infection as being symptomatic or asymptomatic. Those additional investigations should be performed within the first 4 weeks of life in order to be able to offer treatment within the optimal window of opportunity.

Clinical examination

All congenitally infected neonates should be thoroughly examined at birth for the most common signs of cCMV infection: small for gestational age, hepatomegaly, splenomegaly, petechiae, microcephaly and jaundice/ hyperbilirubinemia. If any of these symptoms is found, the child is considered symptomatic.

Many other signs and symptoms at birth have been reported in case reports, such as respiratory distress syndrome, congenital nephrotic syndrome, nephritic syndrome, hypothyroidism, cardiac problems, intestinal malrotation with positive intestinal CMV biopsy, osteitis and cutaneous presentations such as perineal papules erosions and ulcers.

Laboratory testing

Laboratory testing should be performed with hematocrit, leucocyte and thrombocyte count, AST (aspartate-aminotransferase) and ALT (ala-aminotransferase). Determination of the viral load can be performed although its clinical value remains unclear. Although there seems to be a higher viral load in symptomatic infants compared to asymptomatic infants, no clinically relevant relation between viral load and neurodevelopmental or hearing outcome has been described so far (17). Further studies on the significance of blood viral load are warranted.

Cranial Imaging

Since cCMV can affect the central nervous system (CNS), a thorough assessment for CNS involvement is necessary. Experts agree that every child should have at least a cranial ultrasound at birth. Whether or not MRI should also be performed in every child, remains unclear (18). Although a cranial ultrasound performed by an experienced pediatric radiologist or neonatologist is very effective in showing cystic lesions, calcifications, ventriculomegaly and cerebellar abnormalities, other abnormalities (white matter lesions, polymicrogyria, lissencephaly, hippocampal dysplasia and cerebellar hypoplasia) are better detected by MRI (10). Although no international consensus exists on the use of both MRI and cranial ultrasound in the diagnostic work-up of all children with cCMV, we believe that MRI provides valuable additional information on central nervous system involvement and that it could be beneficial to perform both in every neonate with cCMV. Recently, a new MRI severity score was published helping with early prediction of long-term neurological sequelae (19).

Hearing screening

Sensorineural hearing loss (SNHL) is the most common problem in cCMV with up to 20% of asymptomatic newborns having congenital or late-onset SNHL (20). Therefore, all CMV-infected infants should have an audiological screening, preferably by auditory brainstem response. Any deviation of ³ 20 dB is considered abnormal and should be evaluated by an ear-nose-throat specialist.

Ophthalmologic screening

In all infants with cCMV a fundoscopy should be performed to detect chorioretinitis and/or optic atrophy, which occurs in about 10% of symptomatic babies (21).

Classification asymptomatic and symptomatic cCMV

After all investigations have been performed, the classification symptomatic/asymptomatic can be made based on all results. This classification has an impact on the decision for treatment, the way follow-up is planned and the way parents are counselled concerning long-term outcome. According to the literature, about 10-15% of live-born infants with cCMV are classified as symptomatic after birth.

Recently, it was suggested that the symptomatic children should be classified as mildly, moderately or severely symptomatic (18). It is essential that a uniform definition of symptomatic and asymptomatic cCMV infection is used worldwide. Whether SNHL should be part of this definition remains a matter of debate amongst various research groups. Being the most common sequela, SNHL should be included in the definition of symptomatic cCMV according to recent American guidelines (22).

Figure 1 describes the criteria for classification in mildly, moderately and severely symptomatic cCMV as adapted from the European expert consensus statement in 2017, with isolated hearing loss being part of this criteria (18).

Therapy

Every (severely) symptomatic child is eligible for treatment with valganciclovir. Almost 20 years ago Kimberlin et al. published the first clinical trial on anti-viral treatment of infants with symptomatic congenital CMV infection. The infants were treated with ganciclovir 6 mg/kg/dose every 12 hours intravenously for 6 weeks. Despite significant loss to follow-up, 21 of 25 treated infants (84 %) showed either amelioration or normalization of hearing loss versus 10 of 17 infants in the control group (59%). Safety evaluations showed neutropenia as the main toxicity. Additionally, the positive effects of ganciclovir on neurodevelopmental outcome persisted after 1 year of age.

Several years later dose-finding studies for the oral pro-drug of ganciclovir, valganciclovir, were performed. Oral dosage of 16 mg/kg/dose valganciclovir every 12 hours showed a comparable pharmacokinetic profile compared to IV ganciclovir. The major advantage of this administration route is the fact that there is no need for a central venous catheter and therefore, no need for hospitalization during treatment.

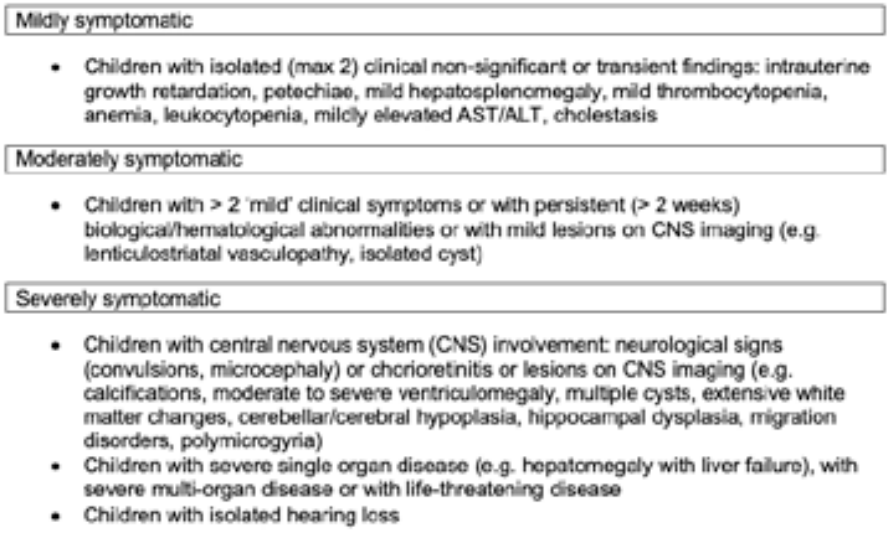
The possibility to give oral medication also re-opened the discussion on the duration of therapy. Kimberlin et al. suggested that the positive effect of 6 weeks of antiviral treatment seemed to wane over 2 years. They observed that viral loads became detectable again shortly after cessation of therapy. Studies indeed suggest that hearing outcomes at 24 months are better if complete viral suppression is achieved within 14 days after starting treatment and maintained for the rest of the treatment. However, clinical relevance of this effect has been questioned (17).

A randomized controlled trial addressed the question whether 6 months of valganciclovir was superior to 6 weeks of treatment. Although best-ear hearing after 6 months was similar in both groups, hearing was more likely to improve or to remain normal at 12- and 24-months follow-up in the group having received 6 months of therapy (73%) versus 6 weeks of therapy (57%, $p = 0.01$). Additionally, the group that was treated for 6 months had better neurodevelopmental scores at 24 months (evaluated by Bayley-III). Severe neutropenia was comparable in both groups and reversible in all cases (23). Since the intended effect of treatment (amelioration of best-ear hearing and amelioration of neurodevelopmental outcome) is more convincing in the 6-month treatment group, current state of the art is to treat infants for 6 months with valganciclovir, unless severe side effects necessitate an earlier discontinuation.

Of importance is that all studies were performed exclusively in infants with a gestational age above 32 weeks who were less than 1 month old when treatment was started.

For asymptomatic infants, expert consensus remains not to treat the infection in order to avoid exposure to the potential risks of valganciclovir administration, such as neutropenia, liver dysfunction (mostly transient) and possible gonadal toxicity and carcinogenicity (observed in animal models). However, since asymptomatic infants also show a risk of hearing deterioration, research is needed to explore possible treatment strategies for these children. Recently, a retrospective cohort study including infants and children with asymptomatic cCMV and later hearing loss, who received treatment with valganciclovir after the neonatal phase (mean age at start of treatment 53.3 weeks, range 12-156 weeks) showed best-ear hearing improvement in 90.8% of treated infants. Short-term adverse effects were limited (only 4.4% transient hematological changes), and long-term adverse effects were not reported (24). In this context, the results are awaited from an ongoing phase 2 open-label trial (ClinicalTrials.gov Identifier: NCT03301415 - USA), in which asymptomatic infants are treated with valganciclovir during

Figure 1 : *Criteria for classification in mildly, moderately and severely symptomatic cCMV (Adapted from the European expert consensus statement in 2017 (18))*



4 months in order to prevent later hearing loss.

Long-term outcome

Disabilities due to cCMV are estimated to be more common compared to any other well recognized conditions such as Down syndrome, spina bifida or fetal alcohol syndrome (25). Around 20% of infected neonates will suffer neurodevelopmental and/or audiological sequelae. Both symptomatic as well as asymptomatic children can develop sequelae, with a higher risk in the symptomatic group (Figure 2). Approximately 40% to 60% of infants with symptomatic cCMV will have permanent sequelae due to the disease: most commonly SNHL, followed by cognitive impairment, chorioretinitis and cerebral palsy. In infants with asymptomatic cCMV at birth, 10-15% will develop sequelae, mainly SNHL. Conflicting results are published concerning the risk of having neurodevelopmental and behavioral problems in infants with asymptomatic cCMV (26, 27). Additionally, no predictors of adverse outcome in asymptomatic cCMV could be identified (1, 25).

Sensorineural hearing loss

Hearing loss is the most common sequela in both symptomatic and asymptomatic cCMV. It is unclear whether late-onset SNHL is caused by viral reactivation or by the immunological host response. A review by Goderis et al. showed that 12.6% of all children with cCMV (1/3 of symptomatic children and 1/10 of asymptomatic children) experience hearing loss. Among symptomatic children, the majority have bilateral loss. In the asymptomatic group unilateral hearing loss is more common.

SNHL in cCMV infected children is characterized by fluctuations, progression and often delayed-onset. It can be unilateral or bilateral and can be severe to profound with need of hearing amplifications or cochlear implants. About 6% of infected children need a hearing aid or cochlear implant ranging from 29-44% to 1-3% in symptomatic and asymptomatic neonates, respectively (1).

The risk of delayed onset and progression of hearing loss in all cCMV children emphasizes the need for a long-term follow-up. Timely diagnosis and management is essential to improve hearing outcome (25).

Neurodevelopmental outcome

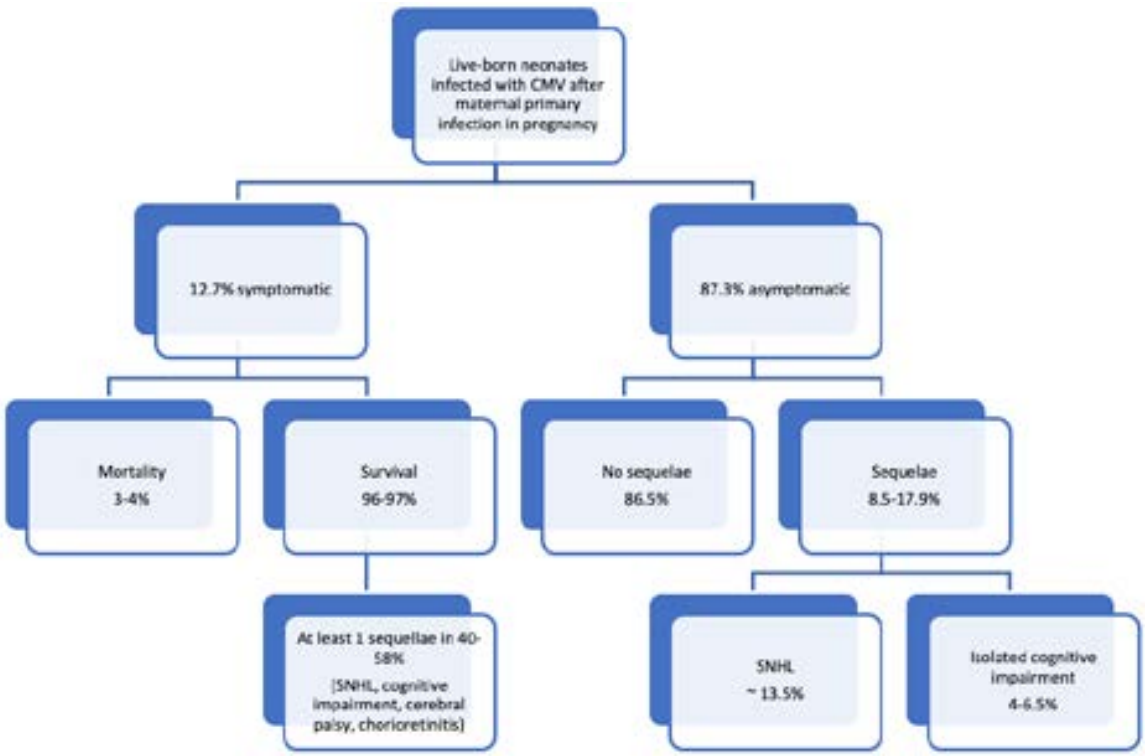
Congenital CMV is the leading infectious cause of neurodevelopmental delay: compared to CMV-negative children, CMV positive children are twice as much at risk to develop long-term impairment up to the age of 6 years (28). Cognitive impairment (mental delay, speech impairment), motor impairment (cerebral palsy, fine motor problems, epilepsy, hypotonia) and neurobehavioral impairment (autism spectrum disorder, attention deficit disorder) have all been described in children with cCMV. Since children with hearing loss have a higher risk of developing vestibular dysfunction, this may also cause motor problems. An interesting finding is the suggestion of a relationship between autism spectrum disorders and cCMV. However, a meta-analysis in 2018 could not confirm this association (29). Further studies on this topic are warranted. Presence of severe abnormal neonatal imaging (MRI and cranial ultrasound) is most predictive for poor outcome. It also has been suggested that gestational age at seroconversion and the classification at birth might correlate with outcome (1). cCMV infection seems to be more severe in newborns born to pregnant women with first trimester infection and if classified as symptomatic at birth. However, both symptomatic and asymptomatic newborns with cCMV infection can develop long-term sequelae, particularly in the behavioral and communicative areas, independently from the trimester of maternal infection (27). This is important in counselling parents.

Topics of discussion

Primary versus non-primary infection

For a long time, primary maternal infections were assumed to have a more significant impact on the fetus than non-primary infections. More recent data, however, have indicated that preconceptional maternal presence of CMV IgG is not protective against CMV-infection related fetal damage or later hearing loss. Differences in natural history and long-term prognosis of cCMV disease according to maternal primary versus non-primary CMV infection are not clearly documented (30, 31). Results from a recent meta-analysis indicate that neither symptomatic infection at birth nor the development of long-term sequelae were significantly correlated to the type of infection (32). Although

Figure 2 : *Frequency of sequelae in infants with cCMV after primary maternal infection. (Adapted from Leruez-Ville et al (2020) and Dollard et al (2007)) (1, 35)*



preconceptional seroimmunity might provide protection against intra-uterine transmission of CMV, once fetal infection occurs the risk of developing symptoms and sequelae is similar in both primary as well as non-primary infection (31).

Universal versus targeted screening

Alternative technologies for universal screening are currently evaluated. Due to widespread utilization in neonatal screening for other conditions, there has been much interest in using dried blood spots (DBS) taken at birth for CMV screening. However, screening DBS is less sensitive than PCR testing of saliva, with a sensitivity ranging between 28 and 100%, and is contingent upon the method of extraction and DNA amplification and the patient group selected. The recent standardization of viral DNA extraction and innovative PCR techniques have led to improved sensitivity of DBS screening to around 80%. A potential limitation in the use of DBS is that only 80–90% of congenitally infected infants have detectable CMV in their blood soon after birth. Despite this, the sensitivity of DBS screening has been shown to adequately detect those infants most at risk of developing SNHL. Stored DBS can be used to diagnose cCMV retrospectively (3, 33).

An alternative approach could be testing infants who do not pass their newborn hearing screening. A large-scale study led to identify 57% of the infants with CMV-related SNHL in the neonatal period. Additionally, the costs associated with targeted neonatal screening look favorable compared with other screening programs. However, this targeted approach would miss those CMV-positive infants who pass the newborn hearing test but are still at risk for late-onset SNHL (34).

The development of new techniques such as quantitative nucleic acid amplification tests (QNAT) and the generalization of PCR assays on urine or saliva samples, less expensive and less affected by transport and storage, could be the most effective approach for use in widespread newborn screening programs (16).

Conclusion

Congenital CMV is the most common congenital infection worldwide with an important impact on child, parents and society. Although many questions regarding this disease were answered, many topics are still under discussion and remain to be explored.

It is of utmost importance that when a child is diagnosed with cCMV, all additional investigations are performed in a timely manner so that therapy can be offered if eligible. A thorough follow-up until the age of 6 years, both audiologically and neurodevelopmentally, is recommend in every child with cCMV. Ideally, investigations and follow-up should be performed in a center with experience on cCMV.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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