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Maternal and Congenital Cytomegalovirus (cCMV): A Review Article

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Abstract
Cytomegalovirus is the leading cause of congenital infection. Among them 85 to 90% are asymptomatic during antenatal period while 7 to 12% are symptomatic which is more common during neonatal period. The most common cause of cCMV through vertical transmission primary from mother to its foetus during antenatal period: sensorineural hearing loss, ophthalmological impairment as well as neurodevelopment deficiencies in the neonates. There is no generally recognised procedure for screening for potential cases of cCMV in pregnant women or in all newborns. Only those who have been identified as at risk are currently screened during pregnancy, and when a congenital infection is suspected, foetal and/or neonatal testing is performed. Although there are still certain obstacles to overcome, knowledge about prevention, screening, and treatment has grown recently. Through targeted information initiatives, awareness among pregnant women and the broader public needs to be raised. Concluding the evaluation of a universal serological prenatal screening has been spurred by the availability of valaciclovir therapy throughout pregnancy, when suitable.

Keywords: Congenital, Cytomegalovirus, Maternal, Neonatal.

Introduction

One of the main causes of birth defects and developmental disabilities is congenital cytomegalovirus (cCMV) infection, which is transmitted from mother to foetus during pregnancy. The most frequent cause of congenital infections is CMV.[1]The disease is asymptomatic 85–90% of the time. The primary maternal infection during pregnancy is usually followed by the symptomatic congenital disease. In the early neonatal period, symptomatic cCMV carries a mortality risk of up to 7 to 12%, despite being much less common. CNS damage increases the risk of severe morbidity, which includes hearing loss, vision impairment, and neurodevelopmental delays. Since 10 to 15% of asymptomatic diseases develop long-term morbidities, they are not completely benign.[2,3]

Therefore, there is no generally recognised practice for screening in all pregnant women. Only those who have been identified as at risk are currently screened during pregnancy, and when a congenital infection is suspected, foetal or neonatal testing is performed. As a result, most infections are identified during or after birth.

Epidemiology

The virus can spread to the foetus through the transplacental route during pregnancy, through direct contact with cervicovaginal secretions or blood during labour and delivery, or through breast milk after delivery.[4] A woman's chances of giving birth to a child with symptoms are between 3.9 and 5.2% if she has primary CMV during the first trimester.[5] Following the mother's primary CMV infection in various trimesters, comparable patterns of vertical transmission and severe foetal impairments were noted. It is unknown currently, though, if congenital CMV infection in the second or third trimester causes any additional long-term negative consequences. Babies should be followed up for longer-term hearing and neurodevelopmental outcomes, and foetuses with infections in the later trimester should still be watched for growth restriction.[6]

In developing nations, the prevalence of cCMV is higher, ranging from 1% to 5%. However, it is challenging to identify the disease because only 10% of newborns exhibit symptoms. Babies with symptoms are more likely to experience long-term neurological consequences, with 40–58% of them going on to develop permanent sequelae like sensorineural hearing loss, ophthalmological deficiencies, and neurodevelopmental delays. About 13% of newborns with cCMV exhibit symptoms at birth, and 20% of newborns have long-term consequences. This number includes 13% of newborns who exhibit symptoms at birth and an additional 7% of newborns who do not.[7]The most prevalent birth symptoms in infants with cCMV after maternal PI during pregnancy include: hepatosplenomegaly, purpura, microcephaly, seizures, chorioretinitis, intrauterine growth retardation, jaundice, and thrombocytopenia.[8] Among permanent sequelae, the most common are sensorineural hearing loss (SNHL), which is more frequent in symptomatic cCMV infections.[9] as well as long-term physical and mental impairments.[10]

Sign and Symptoms

The International Congenital Cytomegalovirus Recommendations Group recently attempted to categorise the various cCMV severity levels.[10] according to the clinical signs and symptoms of cCMV infections. These symptoms included: (i) a variety of clinical manifestations, including hepatosplenomegaly, intrauterine growth restriction, and thrombocytopenia; (ii) involvement of the central nervous system (CNS), as demonstrated by microcephaly and neuroimaging changes, including cerebral calcifications, ventriculomegaly, periventricular echogenicity, and seizures.[11] Therefore, cCMV infections were categorised as either (i) moderately to severely symptomatic, when referring to multiple clinical manifestations, or (ii) mildly symptomatic, when referring to just one or two symptoms or syndromes, in order to provide guidelines for antiviral treatment.[12]

Screening

Maternal: Both primary and non-primary maternal CMV infections during pregnancy are frequently asymptomatic. Only one-third of the cases have the non-specific symptoms, which include flu-like syndrome, myalgia, asthenia, and mild fever. In half of the cases, non-specific laboratory results are found, primarily as elevated liver enzymes and lymphocytosis greater than 40%.[13] Only pregnant women who exhibit suggestive clinical symptoms or signs during antenatal ultrasound scans are eligible for testing. Pregnancy-related serology screening is based on IgG and IgM testing, with IgG avidity testing conducted if IgM is positive.[14] This approach is not advised since doing a second IgM test to confirm the first result after two weeks could postpone the diagnosis and the ensuing treatment. Because anti-CMV IgM has no specificity for recent primary infections, its presence in a pregnant woman's serum should not be taken as

a guarantee of vertical transmission. It is important to remember that IgM antibodies may develop because of cross-reactivity with other viral infections or may last for a long time. Therefore, to accurately assess and confirm the presence of an active CMV infection, additional diagnostic measures should be used. To rule out or confirm a recent primary infection, it is advised to request IgG avidity testing if positive IgM is found. A primary infection within the last three months is indicated by a low avidity IgG, whereas an infection that happened more than three months ago is indicated by a high avidity IgG. In about 0.5% of all women who are screened, the avidity test may produce inconclusive results.[15]

Varies Invasive and Non-invasive methods for screening of CMV during Pregnancy

- **Amniocentesis:** The method of choice for diagnosing foetal infection is amniocentesis, which involves detecting and quantifying viral DNA in amniotic fluid (AF) using qPCR between 8 weeks after the mother's primary infection began and 20–21 weeks of gestation.[16]
  - Less than eight weeks after the mother's infection and before eighteen weeks of pregnancy are when most false-negative diagnoses occur. In addition to viral presence, the amount of viral CMV found in amniotic fluid is directly correlated with the severity of the infection and foetal involvement. A value below 103 most likely rules out a serious infection and future foetal symptoms, whereas a result above 105 genome equivalents indicates a severe form of foetal disease.[17]
  - Furthermore, scientists have looked for and detected proteins in amniotic fluid that may indicate foetal illness. The amniotic fluid of seriously infected foetuses has been found to contain a few proteins that are involved in the immunologic and inflammatory response. A severe form of the disease with neurologic and cerebral damage is indicated by the abnormal amount and preponderantly inflammatory response observed in the placental sample, amniotic fluid, and maternal–fetal barrier.[18]
- **Cordocentesis:** A second invasive method for diagnosing cCMV could be cordocentesis, but given the risk to the foetus, it is not advised. Nevertheless, since ultrasound (US) results are typically normal in most foetal infection cases at prenatal diagnosis.[19]
- **Blood Investigation:** Haematologic, virologic, and biochemical testing could offer helpful prognostic indicators for distinguishing between symptomatic and asymptomatic cCMV.[20]
  - The most prevalent kind is antibody serum detection. Antibody serum detection is the most common type of diagnosis. Primary infection is characterized by the presence of immunoglobulin M (IgM) antibodies in the patient’s serum, which are detected as early as four weeks following primary infection and may persist for a maximum of 20 weeks. Blood viral DNA is commonly found in positive patients together with IgM antibodies of diagnosis.
  - Primary infection is characterized by the presence of immunoglobulin M (IgM) antibodies in the patient’s serum, which are detected as early as four weeks following primary infection and may persist for a maximum of 20 weeks.
  - Blood viral DNA is commonly found in positive patients together with IgM antibodies.[21]The best virologic markers were DNAemia (above 30,000 copies/Ml) and a high level of IgM antibody index (by ELISA), while the best nonviral markers were β2-microglobulin (above 11.5 mg/L) and platelet count (below 50.000/Ml).[20]
- **Ultrasound Scanning:** Imaging using ultrasound. US imaging, the foundation of non-invasive prenatal diagnosis, can identify cCMV in approximately 15% of cases by identifying placentitis, oligohydramnios, hepatosplenomegaly, and other subtle findings. When cCMV infection is present,

US examination can be used to predict normal neurodevelopmental outcomes as well as to monitor foetal abnormalities.

However, after 30 weeks of pregnancy, the only method that offers 95% sensitivity for identifying CNS abnormalities is the combination of serial US and magnetic resonance exams.[22]

- Congenital CMV (cCMV) affects the development of the foetal central nervous system (CNS), which results in abnormalities of the placenta and amniotic fluid, extracranial abnormalities, and sensorineural hearing loss. Numerous CNS abnormalities may be linked to congenital CMV foetal infection. These can be mild or severe, arise from the brain infection's early inflammatory, destructive, and obstructive processes, and have a direct impact on the prognosis of the foetus. Severe intracranial symptoms may include hydrocephaly, microcephaly (a decrease of less than two standard deviations), ventriculomegaly (greater than 15 mm), and high echogenicity in the periventricular regions. Congenital CMV infection is frequently linked to increased cisterna magna (greater than 8 mm), vermian hypoplasia, periventricular cysts, corpus callosum agenesis, lissencephaly, and porencephaly.
- Additionally, a USG can be used to detect abnormalities of the digestive tract, such as hyperchogenicity of the bowel, and to rule out spleenomagaly, pleural effusion, hepatosplenomegaly, and abnormal cardiac development, such as cardiomegaly or calicifaction.
- There are certain placental abnormalities that manifest after 20 weeks of gestation and are characterised by a heterogeneous appearance, placentomegaly, and calcification during the 12 weeks of maternal infection. d abnormal cardiac development like calicifaction or cardiomegaly. There are certain placental abnormalities that manifest after 20 weeks of gestation and are characterised by a heterogeneous appearance, placentomegaly, and calcification during the 12 weeks of maternal infection.[23]

Neonatal: A positive CMV DNA PCR in urine or saliva obtained within 3 weeks of birth is the basis for a confirmed diagnosis of cCMV.[24]Saliva may be falsely positive even though both fluids exhibit the same sensitivity because saliva samples may be contaminated by a small amount of CMV DNA from breast milk. Because of this, it is advised that the sampling procedure be carried out an hour after breastfeeding, and any encouraging findings should always be confirmed by a follow-up urine sample. Nonetheless, false positive cases were easily distinguished from true positive cases, which displayed extremely high viral loads, due to their lower salivary viral loads.[25]

An entirely different natural history and set of aftereffects could result from a positive CMV DNA PCR obtained after 21 days of age, which could indicate postnatal acquisition of infection. In these situations, a retrospective diagnosis of congenital versus postnatal infection can be made by analysing the CMV DNA in the newborn's dried blood spot. The sensitivity of this test is 85.7% (95% CI 74.3–92.6).[26] and aids in giving families an explanation for clinical characteristics that manifest evidently after three weeks of age. Delays in diagnosis, however, result in lost chances to improve outcomes for neonate who qualify for antiviral therapy.

Because of this, the first step is to look for CMV DNA and determine whether a congenital infection is present. Congenital infection must be ruled out in foetuses with IUGR that cannot be explained in any other way, in neonates who fail universal hearing screening (suspicions of sensorineural hearing loss), and when suggestive neonatal symptoms or signs, such as microcephaly, are found.[27,28] Similarly compared to universal screening programs, hearing-targeted newborn programs are more prevalent and restrict cCMV screening to infants who do not pass their newborn hearing screening.[29] However, without antenatal and/or

neonatal screening programs, the majority of cases (95%–99%) of cCMV at birth go undetected, resulting in lost opportunities.[27,28]

Prevention And Treatment

Maternal: Patients who are seronegative should prevent infection both before and during pregnancy. Maintaining good hygiene greatly reduces the chance of contracting an infection.[30] These include not kissing children on the mouth or cheeks, sharing cutlery, food, drinks, washcloths, etc., and washing your hands after handling young children's bodily fluids and surfaces they have touched, such as toys, high chairs, strollers, etc. Maternal infection during 11–12 weeks of pregnancy is considerably reduced by an intervention centred on the identification and hygiene counselling of pregnant women who test negative for CMV.[31]

Hyperimmunoglobulin can be used to reduce the risk of foetal infection and disease when the mother's infection was discovered periconceptionally, during the first trimester, or in the early second trimester.[32] Even that it has been shown to reduce foetal disease cases in terms of infection and clinical abnormalities, the administration of hyperimmunoglobulin during the first 20 weeks of pregnancy is thought to be advantageous, especially in cases of CMV primary infections. There is disagreement regarding the advantages of administering treatment after 20 weeks of pregnancy.[33]

Neonatal: Avoiding symptoms and reducing foetal lesions and organ involvement should be the main goals of management when foetal transmission is suspected.[34] Immunoglobulin therapy dramatically reduces and prevents the risk of foetal clinical disease after transmission and amniotic viral detection.[35] Given the low concentration of immunoglobin attained through placental passage, cordocentesis should be used to administer hyperimmunoglobulin for optimal outcomes rather than maternal perfusion.[36]

Drugs, especially ganciclovir, valganciclovir, and valacyclovir, have been studied in pregnant women and infants, even though no antivirals are specifically licensed for the treatment of cCMV. When administering antiviral therapy during pregnancy, caution is taken to account for both drug efficacy and toxicity. Valaciclovir has been the focus because of its high bioavailability and adequate amniotic concentrations when taken orally. In cases of maternal primary infections in the first trimester, a dose of 8 mg per day has been shown to be both safe and effective in lowering the risk of foetal illness when compared to a placebo. It can lower the risk of congenital CMV infection and pregnancy termination when given early in gestation following maternal infection. Regretfully, in the case of the pregnant woman's periconceptional infection, the effectiveness was not statistically significant.[37]

Conclusion

In conclusion, it only applies to primary maternal infections, and universal prenatal CMV screening is necessary to identify pregnant women with primary CMV infections and neonates. Immediately following diagnosis and in the early stages of pregnancy, strategies to reduce foetal involvement—such as the use of hyperimmunoglobulin and antiviral medication—are essential due to the foetal sequelae. This limits the potential of antiviral (valacyclovir) treatment during pregnancy to reduce maternal to foetal CMV transmission. The most effective ways to avoid congenital CMV (cCMV) and its related complications are screening and good hygiene.

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