



CONGENITAL CYTOMEGALOVIRUS INFECTION: A REVIEW ON DIAGNOSIS, PREVENTION AND TREATMENT

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ABSTRACT

Cytomegalovirus (CMV) is recognized as the most common congenital viral infection in humans and an important cause of morbidity and mortality in immune-compromised hosts. Children with congenital CMV infection has led to the development of non-genetic sensorineural hearing loss(SNHL).Diagnosis of acute maternal CMV infection by the presence of IgM and low IgG avidity requires confirmation of fetal infection which is typically performed by cytomegalovirus polymerase chain reaction(PCR) of the amniotic fluid. Viral culture of the urine and saliva obtained within the first two weeks of life continue to be the gold standard for diagnosis of congenitally infected infants. PCR assays of dried blood spots from infants have not been shown to have sufficient sensitivity for the identification of most infants with congenital CMV infection. However, saliva PCR assays are currently being assessed as a useful screening method for congenital CMV infection. In the immune-compromised host, newer rapid diagnostic assays such as pp65 antigenemia and real-time CMV PCR of blood or plasma have allowed for preemptive treatment reducing morbidity and mortality. However, lack of standardized real-time PCR protocols hinders the comparison of the data across different centers and the development of uniform guidelines for the management of invasive CMV infections in immune-compromised individuals. This review discuss about the clinical importance of congenital CMV infection, the developments in laboratory diagnostics, and the benefits of antiviral therapy. It also identifies the global efforts still required in the prevention of maternal infection and in the optimization of antiviral therapy to further reduce the burden of congenital CMV disease.

Keywords: Cytomegalovirus (CMV),Sensorineural Hearing Loss (SNHL), Mother-to-child-transmission (MTCT), Polymerase Chain Reaction(PCR),Antiviral Therapy

INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous human specific DNA virus which belongs to Herpesviridae family. The vast majority of CMV infections are asymptomatic or self limited in healthy children and adult[1-3]. This spreads by close interpersonal contact through saliva, placental transfer, blood, genital secretion, breast milk and urine or hematopoietic stem-cell transplantation .This remains the main non-genetic cause for sensorineural hearing loss (SNHL) and delayed neurodevelopment.[4-5].Maternal transmission to fetus of a new or reactivated latent infection can occur at any gestation week ,which leads to congenital CMV. [6]. Though Congenital CMV infection is the commonest congenital infection worldwide ,general population compared to other condition lacks the awareness, which is the main way to prevent fetal infection. Awareness to the pregnant ladies during the ANC visit, good hygiene practices along with hand washing, avoiding the potential sources of CMV .CMV infection can be acquired in the newborn via congenital, intrapartum and antenatal routes of infection. CMV infection of the new born occurs due to secondary exposure to the cervical secretions of infected mother during vaginal delivery or via ingestion of CMV-infected breast milk.[7].Premature babies appears to have high risk for CMV-associated diseases. These infants additionally have the symptoms of worsening respiratory status, pallor, bradycardia, neutropenia and bowel distension at the onset of the infection, regardless the virus was acquired postnatally, from human milk or transfusions.[8-9]

Congenital CMV occurs transplacentally which may result in symptomatic or asymptomatic infection in neonate. Intrauterine CMV transmission may occur in mothers without preexisting immunity who first acquire CMV infection in pregnancy (primary infection).In women with preexisting antibodies to CMV either by reactivation of previous maternal infection or by acquisition of a different viral stain (non-primary infection)[10]. Mostly fetal transmission and symptomatic disease is much greater during a primary maternal CMV infection. CMV seronegative mothers will become most infected during pregnancy [11-12]. During this period infected women will transmit virus to the fetus. Non primary maternal CMV infections can also result in fetal transmission, which may represent activated latent infection or reinfection with a new strain in seropositive women. Clinical findings include hepatosplenomegaly, jaundice, generalized petechie , purpura , hydrops , seizures, sensorineural hearing loss, abdominal distension and hypo calcified enamel.[13-15].

DIAGNOSIS

There is no universal screening for CMV infection in mother or newborns. There are many clinical trials that is on process for the accurate diagnosis.

Pregnant mothers can be diagnosed by using different serological tests by the presence or absence of CMV IgG antibodies. Among these are the complement fixation, Enzyme-linked immunosorbent Assay (ELISA), anticomplement immunofluorescence, radioimmuno assay and indirect hemagglutination [16]. Also it can diagnosed by detection of IgM antibodies, but shows poor co-relation of results obtained with different commercial kits for IgM testing and also lacks specificity for primary infection because of false-positive

results, because IgM can persist for months after primary infection, and because IgM can be positive in reactivated CMV infection.[17-20]

Fetal infection is diagnosed by positive viral culture or Polymerase Chain Reaction (PCR) from amniotic fluid. Diagnosis in the Neonate is made by viral detection in body fluids via. PCR, culture or antigen testing (pp65 antigen) within the first 3 weeks of life. [18]

Although real time PCR technology has led to important advances in the diagnostic possibilities, with it being amenable to automation, low cost and unaffected by sample storage and transport conditions but however according to the recent large scale studies [19-20]. Dried Blood Spots (DBS) real time PCR shows low sensitivity and specificity. But however DBS real time PCR still remains the main utility in the retrospective diagnosis of cCMV infection in children who present with delayed onset sequelae [21-25].

Unlike the real time PCR DBS specimen,5 real time PCR on saliva swabs study conducted by National Institute on Deafness and Other Communication Disorders (NIDCD) CMV and Hearing Multicenter Screening (CHIMES) study produced excellent results both for air dried swabs and for swabs sent to the laboratory in the viral transport medium. PCR assays were preferred without a DNA extraction step, making this method even more practical for universal screening purposes. The excellent analytical sensitivity and the ease of salvia collection in neonates makes this specimen more beneficial for neonatal CMV screening.[26]

Other specimen in detection of CMV infection is urine but it's collection can be complicated by number of factors like inadequate diuresis , loss of samples, contamination. Its application has not been evaluated in large , population based screening programs and has not been compared with a gold standard diagnostic method.[27,28]

PREVENTION

Preventive measures to reduce the congenital CMV infection is implemented at different levels, which includes prevention of maternal infection, prevention of MTCT, early detection and intervention by neonatal screening and neonatal antiviral therapy.

Pre-natal screening by the use of maternal serology is not routinely recommended because of the unavailability of proven specific interventions for pregnant women who experience a primary CMV infection & also the fact that most congenitally infected babies are born to woman experiencing a non-primary maternal infection. Diagnosing a non-primary CMV infection in pregnancy is a challenge, since virology or immunological markers for non-primary CMV infections have not been identified.

Many non-randomized controlled trials between 2005-2013 showed that administration of CMV-specific hyperimmune globulin (HIG) to pregnant women with primary CMV infection could lead to a significant decrease of MTCT & decrease in risk of congenital disease. However, in 2014, first phase II randomized placebo-controlled trial, on the use of virus-specific HIG for prevention of congenital CMV infection were published and revealed that difference in rate of congenital infection between the group of pregnant women who had received HIG & the placebo group was not statistically significant. The study also

showed that the clinical outcomes of congenital infection at birth were similar in two groups, and that the number of obstetrical adverse effects were higher in the HIG group as compared to the placebo group.[29-33] There is a recent study on antiviral therapy in women with CMV infection in pregnancy. It shows the efficacy of high dose oral Valacyclovir (8gm daily) in pregnant women carrying moderately CMV infected fetus. A moderately CMV infected fetus is defined by the presence of one or more measureable extracerebral ultrasound features compatible for CMV infection & or one isolated cerebral abnormality &/or laboratory findings of CMV infection in fetal blood. Result show increase in number of asymptomatic neonates after the use of high dose oral valacyclovir, implying the benefit of this therapeutic approach. The limitation of this study is the small sample size and the study design. [34]

Development of a CMV vaccine is the most promising strategy for addressing the problem of congenital CMV. But the challenge for the development of an effective CMV Vaccine is the complex nature of CMV protective immunity, with the possibility of both reactivation of previous infection and the risk of reinfection with genetically distinct viral strains. An ideal vaccine should have ability to both protect the seronegative women from primary infection and augment the immune response in seropositive women to prevent reactivation or reinfection. Several CMV vaccines are currently being evaluated in a number of clinical trials. A live, attenuated strain of CMV, the Towne strain, has been evaluated as a potential vaccine in a number of studies with risk of CMV infection like in immunocompromised solid organ transplant patients. This vaccine can elicit both the humoral and cellular immune response. The limitation of this study is that it show no reduction in the infection rate in a group of young women with children attending group day care. To improve the immunogenicity of a live virus CMV vaccine, a new approach has been undertaken to engineered recombinant 'chimeras' off the attenuated Towne strain and the less attenuated, low-passage Toledo strain. In addition to the live attenuated vaccines, Purified protein and DNA subunit vaccines are also in clinical trials.[35-37]

To date, the mainstay of preventive measures of maternal infection, and in turn of congenital infection, remains the education of pregnant women regarding sources of exposure and behavioral interventions to limit exposure to CMV. A major source of CMV exposure is represented by young children who may shed CMV in saliva and urine. Therefore, specific behavioral guidance aimed at decreasing the transmission of CMV includes hand hygiene when caring for children, particularly after changing diapers or wiping a child's nose, avoiding kissing children on their mouth and avoiding sharing food, drinks and other utensils that can be exposed to children's bodily fluids[38,39].

TREATMENT

Treatment of congenital CMV infection should be administered to symptomatic infants with central nervous system involvement evidence, including SNHL, and should be considered in infants with serious end-organ disease (hepatitis, pneumonia, and thrombocytopenia). The best option for the treatment of congenital cytomegalovirus is the antiviral therapy which has been sustained for symptomatic infants in last few years. Ganciclovir is specifically used for the treatment of congenital CMV. Recent studies has shown

ganciclovir is safe and well-tolerated when used in newborns.[40,41]It has also been useful in the management of severe ,focal, end -age diseases in infants.Ganciclovir also provides long-term neurodevelopmental benefits in some infants with congenital CMV infection.[42]

Treatment should be started within the first month of life[43].

Based on the research provided by the Collaborative Antiviral Study Group[CASG] from 2003-2013 in different randomized control trial ganciclovir [GCV] 6mg/kg/ twice per day shows improvement in hearing outcome in symptomatic infants with CNS involvement[44]. Studies show that the main drawback of the therapeutic strategies was the development of a clinically significant neutropenia .Whereas in renal impairment infant doses adjustment should be made. A subsequent study by the CASG determined that 16 mg/kg/dose of valganciclovir, the oral prodrug of ganciclovir given twice daily can avoid the need of the intravenous ganciclovir. Notably oral valganciclovir was associated with lower risk of neutropenia as compared with intravenous ganciclovir. The limitation of this study is that there is no evidence of benefit of antiviral therapy in asymptomatic infants. Since they were not mentioned in any of the above studies . The decision to stat antiviral therapy in infants with cCMV infection should involve adequate counseling in regards to potential benefits and the risks of antiviral therapy.[45]

Besides neutropenia there is evidence of carcinogenicity and gonadotoxicity of ganciclovir in some animal models showed on other studies. Since asymptomatic infants represents the vast majorities of infants with cCMV infection. We need the screening programs leading to an urgent understanding of the base management of the infants .Another important challenge in the application of the treatment data is weather antiviral treatment should be offered to the infants with isolated SNHL .The last critical point is the management of the children with isolated late onset SNHL and specifically weather antiviral therapy may be offered beyond the neonatal period to children who develop or present SNHL.

CONCLUSION

Congenital CMV infection is common and is responsible for high burden of disease worldwide. Many clinical trials for diagnostic purposes are on progress based on serology, culture, PCR, antigen testing but the real time PCR on saliva swabs has excellent analytical sensitivity till date and has potential to become the universal neonatal CMV screening technique. But we should also be familiar with the clinical prospect of disease both in mother and newborn. Although CMV vaccination remains the most promising preventive strategy but because of reactivation and reinfection, there still remains a greater challenge in its development. Thus mainstay of preventive measure till date still remains the increased public awareness of the disease particularly among women of childbearing age. Children with cCMV infection are at higher risk for adverse neurodevelopmental outcomes, particularly SNHL.The best therapeutic option is the antiviral therapy which is only used for the symptomatic patient.The drug use is the intravenous ganciclovir and oral valganciclovir.Oral valganciclovir is associated with lower risk of neutropenia and renal impairment as compared with intravenous ganciclovir.Till date main drawback oftherapeutic option remains its limitation the

use in asymptomatic infants. Congenital CMV infection is a common disease but still being under-recognized. Thus it should be considered as a major health problem and there should be major focus on its diagnostic, preventive and therapeutic measures which can finally improves the quality of life.

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