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Congenital Cytomegalovirus Infection Management-New Insights

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Abstract

Congenital Cytomegalovirus (CMV) infection is one of major public health concerns and one of the most frequent congenital infections worldwide. Congenital CMV infection is under-diagnosed in the majority of asymptomatic pregnant women due to its self-limited non-specific symptoms and unimplemented screening program. Primary CMV infections are associated with the highest in-utero transmission at estimated rates of 30–35%. Transmission rate occurs less frequently in secondary CMV maternal infections at approximately 1.1–1.7%. Congenital CMV infection can also go undetected at birth because the affected newborns are often asymptomatic, however, they manifest serious morbidities later in life. There are growing evidences that early diagnosis and treatment of newborns with congenital CMV infection can reduce sensorineural hearing loss (SNHL) and the subsequent long-term neurological and developmental disabilities. There is also increased interest in establishing a prophylactic CMV vaccine that can protect seronegative mothers from primary infection and augment the immune response in seropositive women, in order to prevent CMV reactivation or re-infection. Studies show that liquid-saliva polymerase chain reaction (PCR) assay has high sensitivity “100%" it is more advantageous than Dried blood spots (DBS) in detecting congenital CMV infection and it can be used to screen newborns in the first 3 weeks. Suggestive strategies to reduce the burden of congenital CMV disease are; establishing a screening programme for pregnant mothers, developing prophylactic CMV vaccine, early therapeutic intervention in pregnant women and newborns and use Saliva PCR assay as a new method for neonatal CMV screening.

Keywords: Congenital CMV; Sensorineural hearing loss; Disabilities; Screening programme; CMV vaccine

1. Introduction

The aim of this article is to increase public awareness of the epidemiology of Congenital Cytomegalovirus (CMV) infection and its subsequent longterm serious morbidity in late childhood that includes sensorineural hearing loss (SNHL) and long-term neurological and developmental disabilities. This article is also of particular importance as it outlines potential significant health gains from adopting new cost-effective strategies for early detection and early therapeutic intervention of congenital CMV infection during pregnancy and early infancy. It emphasises the privileges of developing preventative measures in order to reduce the burden of congenital CMV disease morbidities.

2. Case Study

A primigravida mother was diagnosed with acute primary CMV infection during pregnancy, when she developed a petechial skin rash and flu like symptoms, at 25 weeks of gestation. CMV infection was confirmed when both CMV-IgG and IgM found to be positive. The mother, had a seroconversion of CMV-IgG between two serum samples obtained in 2-3 weeks apart, which provided a diagnosis of primary CMV infection. The presence of CMV-IgM suggested a recent infection and the low CMV-IgG avidity test was suggestive of antibody-production induced by acute or recent primary CMV infection. Amniocentesis for detection of CMV-PCR was declined and antenatal ultrasounds were all normal. Antenatal maternal serology for; toxoplasmosis, rubella, herpes simplex, syphilis, Hepatitis B and HIV screen was negative. The

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mother delivered her baby at term, via spontaneous normal delivery. Baby was born in good condition, however, was small for gestational age.

At 24 hours of age baby was found to be lethargic, however, the vital signs and other systematic examination were within normal. Infant's blood, saliva and urine samples were checked for CMV-PCR, along with other viral serology screen, and bacterial blood culture. Lumber puncture and obtaining cerebrospinal fluid (CSF) sample was not successful. In view of maternal primary CMV infection, intravenous (IV) Ganciclovir 6 mg/kg every 12 hours was commenced immediately along with IV broad spectrum antibiotics for suspected sepsis. Congenital CMV infection confirmed as CMV-PCR in urine and saliva was positive and serum viral load was high. IV antibiotics were discontinued after 48 hours as blood culture was negative. Infant demonstrated gradual improvement within 48 hours of Ganciclovir administration and symptoms completely resolved over a course of 5 days. On day 10 of life, the virologist advised to switch IV Ganciclovir to oral Valganciclovir 16mg/kg twice a day, following significant reduction of viral load on repeat laboratory testing. Infant tolerated oral Valganciclovir well without significant side effects. Full blood counts, liver enzymes and kidney function were monitored twice weekly and were within normal parameters. Viral load was also monitored weekly and then on alternate weeks and remained negative. Valganciclovir was stopped after 8 weeks, when viral load remained negative for 2 weeks. Cranial US performed in the first week of life and showed periventricular flare, however, brain MRI at four weeks of age was normal. This child also continued to have annual normal audiology, ophthalmology and neurological checks during childhood.

3. Discussion

3.1 Epidemiology

Congenital CMV infection is generally acquired very early in life, it is associated with the highest intrauterine transmission rates at 30–35% [1]. Congenital CMV is one of the most frequent congenital infections worldwide, the estimated incidence of 7 in 1000 of live births, the approximate rates is 0.5 to 2% of all deliveries in the developed world, whilst the transmission rates in the developing countries is higher at around 4% [1-3]. Primary CMV infections are usually asymptomatic but may present with non-specific symptoms in around 10% of patients. Preconception immunity significantly decreases the chances and the severity of congenial CMV infection. Studies show the rate of in-utero transmission in mothers with preexisting CMV immunity is around 1.1–1.7%, whilst the transmission rate is approximately 35% in non immune mothers[1-3]. Approximately 8% of infants diagnosed with congenital CMV disease are born to seropositive mothers whilst it is around 25% in those born to seronegative mothers. The older the gestational age, the higher the rate of vertical transmission, however, the risk of foetal damage is higher when CMV infection occurs in the early stages of pregnancy. First-trimester maternal CMV infections results in adverse long-term morbidities, approximately 20–25% of those infected infants develop sensorineural hearing loss, and up to 35% develop neurological and developmental sequelae. Neonatal mortality rate secondary to congenital CMV infection is around 5-10%. Approximately 9.6% of children diagnosed with cerebral palsy were CMV positive on routine DBS-based screen [6-8].

3.2 Route of CMV transmission

CMV infection can be transmitted by close contact via mucosal surfaces through infected saliva, or other bodily fluids including semen[8-10]. Vertical CMV transmission can occur; intrauterine, intrapartum or post-natal. Intrauterine (mother-to-child) transmission is the most common route that leads to congenital CMV infection due to direct infection of the placenta and amniotic fluid. Newborns can acquire CMV infection during delivery through the intrapartum route, nearly 10% of seropositive mothers shed CMV in the genital tract at the time of delivery. Infants can also acquire CMV infection in the postnatal period through breast milk. CMV infections acquired only during delivery or via breast milk can cause sepsis like illness in low birth-weight newborns and premature infants; however there is no strong evidence to suggest that it affects the future neurodevelopmental outcome [10-11].

3.3 Prenatal CMV screening and diagnosis

Currently, maternal testing for CMV serology is not routinely recommended due to the unavailability of proven specific interventions for pregnant women with a primary CMV infection. Maternal seroconversion of CMV-IgG between two sequential serum samples, 2-3 weeks apart provides the most accurate diagnosis of CMV infection. The presence of CMV-IgM alone has a low specificity and only suggests a primary or reactivation of CMV infection, it can remain positive for several months after primary infection and there is also non-specific cross-reactivity. The presence of both CMV IgM and IgG antibodies does not distinguish between primary and secondary infection, however, it indicates a recent infection. The CMV-IgG avidity test measures the binding capacity of CMV-IgG antibodies, hence it is a useful tool for dating the time of CMV infection. High avidity IgG indicates infection more than 6 months, whereas low avidity IgG along with presence of CMV-IgM indicate antibody-production induced by recent CMV infection within the last 3 months [12-13].

When foetal infection status is unknown, serial antenatal ultrasound can predict congenital CMV infection. The most common foetal ultrasound findings in CMV infection include; ventriculomegaly and hyperechogenic bowel, however, negative scans cannot exclude CMV infection. The foetal brain MRI is highly sensitive and can identify minor changes in white matter, however these changes could represent a reversible inflammatory reaction, and might not affect the long term neurodevelopment. Amniocentesis remains the most sensitive "but invasive" method for the detection of CMV-DNA and confirmation of foetal CMV infection, high CMV viral loads are usually pathognomonic. Amniocentesis should be performed after 21 weeks of gestation, due to the low sensitivity of the test prior to 20 weeks gestation, and at least 6 weeks following suspected maternal infection due to the lag period from the onset of infection to the time of viral shedding into amniotic fluid [14-17].

3.4 Neonatal CMV screening

CMV is excreted in large amounts in urine, however, there is difficulties in collecting urine sample in infancy. Saliva sample is much easier to obtain, liquid-saliva PCR assay sensitivity is 100% and specificity is 99.9%, the rate of false positive results is less than 0.03%. The ease of saliva collection in neonates and the high sensitivity of the test, make this specimen more advantageous for neonatal CMV screening in the first 3 weeks of age, and likely that more asymptomatic infants will be identified. The sensitivity of the Dried blood spots (DBS) screening test varies between 35% to 85%, as not all infants with congenital CMV infection have detectable viraemia at birth, therefore, a negative DBS CMV-PCR result does not rule out CMV infection, whilst the positive test can confirm congenital CMV infection [23-24].

3.5 Postnatal diagnosis

Congenital CMV infection is defined as the presence of CMV in any secretions within the first 3 weeks of life. The diagnosis of CMV infection in neonates is based on virus isolation by PCR to detect CMV-DNA in urine, blood, saliva and cerebrospinal fluid (CSF) within 3 weeks of age [23-24]. Some studies suggested that the amount of CMV copies in blood correlates directly with neurological outcome in symptomatic and asymptomatic patients at birth. The demonstration of CMV-IgM antibodies in the newborn serum is indicative of CMV infection, as maternal IgM antibodies can't cross the placenta, while CMV-IgG antibodies in infancy are mostly maternally transferred antibodies. A rapid test to detect CMV antigen in blood can be performed but the sensitivity is low [25-28].

4. Congenital CMV infection acute clinical presentation

The clinical presentation of congenital CMV infection at birth varies widely, from the complete asymptomatic infection, non-specific symptoms, to potentially life-threatening fulminate disease. The majority of infected infants 85–90% are asymptomatic at birth and only 10–15% are born with symptoms [30-35].

CMV causes inflammatory infiltrate and damages vital organs, focal necrosis can be seen in many vital organs; brain, retina, epithelial cells of the vestibulae, cochlear, semi-circular canals, liver, lung and kidney tissue. The common acute disease presentations include; sepsis like symptoms, jaundice, petechiae, hepato-splenomegaly, chorioretinitis, microcephaly and intracranial calcifications. Other congenital CMV complications include; intrauterine growth retardation (IUGR), prematurity, non-immune hydrops, cerebral ventriculomegaly, intracranial haemorrhage and hydrocephalus. Common laboratory findings include neutropenia, thrombocytopenia, direct hyperbilirubinemia, transaminitis and high CSF protein >120mg/dL. Average neonatal mortality rate is around 5-10% and is usually due to bleeding and hepatic failure. Other less common symptoms include; pneumonia, osteitis, congenital clubfoot and clasp thumb deformity [28-30].

5. Congenital CMV disease long term prognosis

Estimated 40-60% of symptomatic infants suffer from severe long-term neurological and developmental sequelae, approximately 50% of the infected cohort suffer SNHL, visual impairment occurs in around 35% of the cases, and up to two-thirds of patients suffer of cognitive deficits. Approximately 10-20% of asymptomatic patients in the neonatal period, have neurological sequelae and SNHL in late childhood.

SNHL is the most frequent long-term complication; approximately 25% of SNHL in children is attributable to congenital CMV. Overall nearly 10% of asymptomatic and 50% of symptomatic infants develop some degree of SNHL, which is making congenital CMV infection the most common leading non-genetic cause of SNHL in children. Symptomatic patients in the neonatal period suffer SNHL at an earlier age and with greater severity than the asymptomatic cohort. The median age at onset of SNHL is 33 months for symptomatic patients and 44 months for asymptomatic infants. The cause of CMV-induced SNHL is still not clear, it is hypothesised that it is caused by virus-induced labyrinthitis, and a chronic

infection in the CNS or inner ear that continue to be active throughout early childhood. Some studies suggested that a high viral load in early infancy in the urine (450,000 PFU/mL) is highly predictive of SNHL impairment. The immaturity of the immune system in newborns makes them less able to control the infection which leads to progressive nature of SNHL. CMV infected infants may act as reservoirs and continue to shed CMV virus, CMV-DNA has been detected in the perilymph of children with CMV induced SNHL and on those underwent cochlear implantation later in life. Early identification and interventions of SNHL can reduce the functional impairment and improve the receptive and expressive language [28-32].

Microcephaly in neonatal period has a 100% specificity for the prediction of mental retardation and/or major motor deficits. The central Nervous system (CNS) injuries are often irreversible, the mechanism of injury to the developing CNS is still not completely understood, the two main adopted pathogenesis theories are; 1) the CMV produces inflammatory processes and endovascular system injury which can cause necrotic changes and irreversible CNS injury, 2) CMV infection acquired in the first half of pregnancy may have a teratogenic effect in the foetus, it results in neuronal migrational disturbance and disruption in the normal neuronal cells differentiation pathways, which interfere with the normal apoptosis process and subsequently produce malformations. Abnormal brain MRI and in particular detection of intracranial lesions are associated with SNHL, long-term neurological and developmental sequelae and severe intellectual impairment in more than 80% of cases [30-35].

Other long-term consequences include; defects in dentition, optic nerve atrophy and with visual impairment in symptomatic infants. Furthermore, a large proportion of symptomatic infants suffer some degree of psychomotor disabilities [32].

6. Congenital CMV treatment

There are three systemic drugs approved for CMV treatment: Ganciclovir, or its prodrug Valganciclovir, Foscarnet and Cidofovir. Ganciclovir, and Valganciclovir are the most widely used drugs that have been useful in CMV disease management and prophylaxis. The decision to start antiviral therapy in infants with congenital CMV infection should be consider as early as possible along with parents counselling regarding both the benefits and potential side effect of antiviral therapy. The most common side effects of Ganciclovir include; neutropenia, anaemia, and thrombocytopenia. Studies demonstrate that intravenous Ganciclovir 6 mg/kg every 12 hours for 6-weeks can preserve normal hearing and improves hearing outcomes at 6 months, there were also evidences of short-term improvements in terms of head growth, weight gain and resolution of transiminitis. Nevertheless, studies also show that early treatment can reduce developmental delay at 6 and 12 months compared to untreated infants. Valganciclovir recommended dose is 16 mg/kg/dose twice daily, it provides comparable improvement and positive systemic results to Ganciclovir. The simplicity of its adminstration makes it easier to be used at home, reduce hospital stay and also simplifying the management of congenital CMV. It is hypothesised that a longer duration of antiviral therapy has potentially better outcome due to more prolonged suppression of viral replication. Early and prolonged treatment of valganciclovir for 6 months is now recommended as an effective and well-tolerated therapeutic option in symptomatic infants to reduce the longterm CMV sequelae and for a better outcome [36].

Currently there is no much evidence of benefit of antiviral therapy in asymptomatic infants. However there is a recent study evaluated the effect of Ganciclovir therapy on hearing, where the asymptomatic patients with congenital CMV infection showed no hearing loss in the treated group in comparison to 11.1% hearing loss occurring more in those were not treated [37]. Our case also shows that early antiviral therapy has appeared to be useful in ameliorating the severity of end-organ CMV disease in a baby of an infected mother and presented with non-specific symptoms.

7. Congenital CMV prophylaxis

Currently, there is no licensed CMV vaccine despite the growing public health interest. The ideal vaccine should have the ability to protect seronegative women, augment the immune response in seropositive women and prime the immune system to provide protective antibodies in order to prevent CMV transmission to the unborn baby. The government decision about licensing a vaccine will have to be made by the Department of Health's Joint Committee. There are few challenges to develop an effective CMV vaccine; 1)there is many different strains of CMV, being immune to one strain does not stop getting infected with another strain, 2)CMV virus works by evading the immune system and there is assumption that the CMV virus may interfere with the vaccine effectiveness, 3) still more research is required to get clear evidence as to whether it will be safe and effective for mothers to be vaccinated for the first time during pregnancy. The therapeutic strategy to use antiviral therapy in pregnant women is still controversial. A small study carried out to identify the efficacy of antiviral therapy in pregnant women with CMV infection. High dose of oral valacyclovir (8 gm

daily) in women has been tried and well tolerated, it is suggested that it can significantly increased the proportion of asymptomatic neonates at birth (38). Other studies show that CMV hyperimmune globulin (HIG) can be effective if administered during gestation in women with primary CMV infection for both prevention and treatment of foetal CMV infection, however, this is still under clinical development and it has not applied in practice[39-40].

8. Conclusion

Congenital CMV is the most common intrauterine infection worldwide and considered as the most common non-genetic cause of SNHL and neurodevelopmental delay in the late childhood. It is under-diagnosed in the majority of asymptomatic cases during gestation and many asymptomatic newborns. Our case and other studies show that early adminstration of antiviral therapy has deemed to be useful in ameliorating the severity of CMV disease in infants born with non-specific symptoms. Saliva PCR assay is easier method and more sensitive than DBS in detecting congenital CMV infection, as not all CMV infected infants have detectable viraemia at birth. Saliva PCR assay can be used to as alternative method to screen newborns within the first 3 weeks of age. Still more researches are required to develop a CMV vaccine as preventative measure to protect seronegative women from primary infection and also to augment the immune response in seropositive women.

Suggestive strategies to reduce the burden of congenital CMV disease and ensure better outcomes are; establishing a screening programme for pregnant mothers, developing prophylactic CMV vaccine, implementing early antiviral therapeutic intervention in pregnant women and newborns and to replace DBS with Saliva PCR assay for newborns CMV screening.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares that they have no conflict of interests.

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