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Case Report

Congenital Cytomegalovirus Disease after Maternal Non-Primary Infection: Case Report and Review

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Abstract

Objectives: Congenital cytomegalovirus (cCMV) infection is the most prevalent intrauterine infections worldwide and is the leading non-genetic cause of sensorineural hearing loss and neurodevelopmental sequelae. Primary maternal cytomegalovirus infection is generally considered to have a greater risk of transmission and development of severe congenital infection; however, non-primary infection cases, of which physicians are often not aware, can also be symptomatic and develop long term sequelae.

Case Presentation: We report a case of symptomatic congenital cytomegalovirus infection despite preconception maternal immunity. Prenatal care found maternal positive cytomegalovirus (CMV) IgG and IgM, with high avidity of IgG at the first trimester, followed by abnormal fetal ultrasounds. The mother was diagnosed preeclampsia at the second trimester. Cesarean section was done at gestation age 30 weeks due to severely abnormal fetal Doppler flow. Neonatal birth weight 840g, Apgar full, was found jaundice at birth and hearing impairment of left ear. Diagnosis of congenital cytomegalovirus infection was confirmed by newborn urine culture. Valganciclovir was initiated on 2 weeks of life.

Conclusions: Non-primary maternal infection can also end up with symptomatic congenital infection that early administration of antiviral treatment is required. To early aware and diagnose of congenital infection in clinical practice, ongoing efforts are aimed at providing evidence to support a decision-making process in perinatal and postnatal care despite maternal immunity. Also, evaluate effectiveness of antivirus treatment in asymptomatic patient is warranted.

Keywords: *Cytomegalovirus; Fetal Infection; Maternal Immunity; Non-Primary Infection*

Background

The overall birth prevalence of human cytomegalovirus (CMV) congenital infection was 0.64%, but varied considerably among different study populations [1]. At any time during pregnancy, primary (i.e. first infection in life) or non-primary maternal infection (i.e. reactivation of infection or re-infection) can lead to CMV crossing the placenta and infecting the fetus, resulting in newborn disease and long-term sequelae of hearing loss and neurodevelopmental deficits. The protective effect of preconception immunity of the mother is reflected by a much higher vertical transmission rate of primary maternal infection (32.3% vs 1.4%) [1] and is more likely to cause severe symptoms at birth than does non-primary maternal infection [2]. Despite the low transmission rate, non-primary infection is of great concern since most of childbearing- aged women are immune to CMV. In fact, only approximately one-quarter congenital CMV infection were attribute to primary maternal infection in the United States, while three-quarters were born to mothers with non-primary infections [3]. In Shanghai, China, seroprevalence of CMV was 97% among the population age 20 - 25 years old and continued to rise with age [4]. Furthermore, increasing evidences revealed non-primary maternal CMV may also be a significant cause of severe postnatal sequelae and

in some cases, may even cause intrauterine fetal death [5-8]. However, congenital CMV infection is often underdiagnosed and infrequently treated.

In this article, we report a case of symptomatic congenital CMV infection which was confirmed by urine culture on day 4 of life, despite serology test suggested maternal preconception immunity.

Case Presentation

A 30-year-old primigravida had her first prenatal care in health center at approximate 11 weeks of gestation. Routine CMV serologic tests showed positive CMV- IgM and IgG with high avidity. Other routine tests included hepatitis B, syphilis and human immunodeficiency virus infection were all negative. She was referred to obstetrician according to the protocol and risk of congenital infection was explained by the specialty and routine prenatal care was provided. She experienced no complication until the second trimester, when pregnancy induced hypertension and later preeclampsia was diagnosed. Fetal ultrasound at 22 weeks of gestation revealed fetal intrauterine growth restriction (IUGR) and hyperechoic bowel (Figure 1) and deteriorate with increased umbilical artery resistance index and decreased middle cerebral artery resistance index at 26 weeks of gestation. At the same time, the mother was admitted in Obstetric ward for blood pressure control and close observation, received magnesium sulfate, antihypertensive agents and aspirin, and two doses of betamethasone. At last, urgent Cesarean section was performed at 30 weeks of gestation due to severe IUGR and abnormal Doppler.

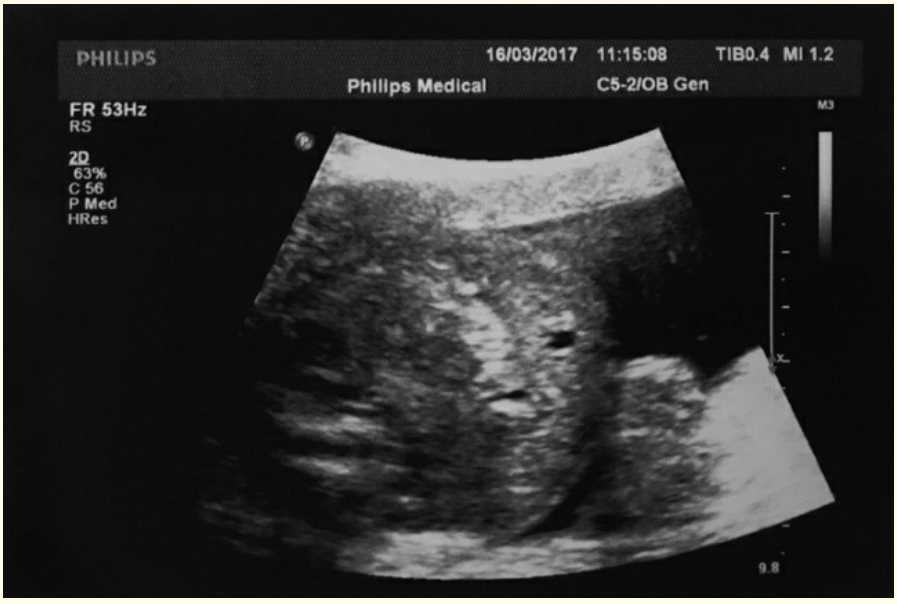

Figure 1: *Fetal hyperechoic bowel.*

Baby was born first, with clear amniotic fluid, Apgar scores were 10, 10 and 10 at 1, 5 and 10 minutes, respectively, with birth weight of 840g (< P10), birth length of 33cm (< P10) and head circumference of 23 cm (< P10). Laboratory investigation on day 2 of life showed positive CMV-IgG and CMV-IgM. Congenital CMV infection was confirmed by urine culture on day 4. CMV DNA was detected (1510 IU/mL) by Polymerase Chain Reaction (PCR) in blood sample on day 20. Meanwhile, jaundice at birth was found (total bilirubin 51 mmol/L, direct bilirubin 9.3 mmol/L) and later developed direct hyperbilirubinemia (total bilirubin 101 mmol/L, direct bilirubin 44.1 mmol/L on

day 45). Full blood count was normal, no thrombocytopenia, no neutropenia. Transfontanelle echography found hyperechoic ventricular walls and cardiac echo revealed patent foramen ovale. Hearing screening of left ear was failed. Ophthalmological assessment was normal. Oral valganciclovir was initiated on 2 weeks of life.

Discussion

Researches support the administration of valganciclovir for 6 months in neonates for benefit of long term hearing and neurodevelopmental outcomes [9]; however, early diagnosis of congenital CMV disease follow non-primary maternal infection is difficult in both prenatal and postnatal period, because of ambiguous interpretation of maternal serology and fetal ultrasound manifestation and non-specific neonatal presentation.

Since the virus is transmitted by mother during pregnancy, diagnosis of CMV infection includes the diagnosis of maternal compartment, fetal compartment and neonatal compartment. Serologically, after CMV infection, CMV- IgG and IgM will become positive. The former one will last for life long while the latter one may persist for months up to one year after natural infection, and is also produced during reactivations or reinfections [10]. To identify primary infection in pregnant women, anti-CMV IgG avidity test is currently the most reliable commercial procedure. IgG antibodies show a low avidity for the antigen during early weeks after the primary infection; however, they progressively mature, initially acquiring moderate and then high avidity. This process reflects the maturation of the immune response, and the high-avidity IgGs are maintained for many years [11,12]. Therefore, low CMV IgG avidity is an accurate indicator of primary infection within the preceding 3 to 4 months, but high avidity is unable to distinguish non-primary infection to past infection, as the case we presented.

The diagnosis of fetal compartment can be studied by non-invasive (ultrasound findings) and invasive (amniocentesis) diagnostic investigation, and should be performed more than 6 weeks after presumed maternal infection and after 20 weeks of gestation [13]. Multiple ultrasonography changes can be found in infected cases, for examples, periventricular calcifications, cerebral ventriculomegaly, hyperechoic fetal bowel and fetal growth restriction. However, the sensitivity of ultrasound is poor and it correctly identifies no more than 20% of infected infants [14]. As in our case, the fetal hyperechoic bowel and IUGR can be the consequences of both CMV infection and maternal preeclampsia, that will confuse or mask the diagnosis of congenital CMV infection. In contrast, amniocentesis for real time PCR provides the optimal means for diagnosing fetal infection. The specificity and sensitivity is usually very good, 92 to 98% and about 90%, respectively [15]. But the pros and cons of this invasive procedure should be discussed individually.

Despite universal screening of all pregnant women to identify those who are CMV-seronegative is not recommended as part of routine antenatal screening [16,17], many general physicians in Macau still order the blood test at the first consultation of antenatal care. Diagnosis of primary CMV infection is straightforward, whereas non-primary infection is not that obvious and lack of universal approach to the ambiguous results. For the mother with positive CMV-IgM and high avidity IgG, some society treat it as past infection and routine prenatal care is given [18-20], while recently others may concern more about the chance of congenital CMV infection and suggested either regular ultrasound or amniocentesis may be considered [10,21,22].

After birth, clinical manifestation of infection varies from asymptomatic to life threatening and most of them are non-specific. The standard diagnostic test is a viral culture in body fluid (e.g. urine, saliva or blood) obtained within the first 3 weeks of life [15,23]. These are convenient and more accurate tests when compare to the prenatal diagnostic method.

Studies reported evidence that universal or target CMV screening improved the outcome of delayed hearing loss in infected infants, and appeared to be cost-effective in United Kingdom and United States [24-27]. However, the cost of testing, the modest efficacy of available antiviral therapy, the high proportion of asymptomatic infections, and potentially adverse psychosocial effects are considered barriers to implementation, and there is not yet any international guideline recommends universal screening. The tests should be ordered only in the suspicious cases.

Same as diagnosis, uncertainty also exists in management of the patient. The current available evidence, including a randomized controlled trial in neonates, found that valganciclovir therapy for 6 months protected against development or progression of hearing loss [9,28]. However, since asymptomatic infants represent the majority of congenital CMV infection and are at risk of developing late-onset sequelae, further efforts would be needed for a proper approach in this population. Great attention has been focused on a potential predictive role of the viral load in peripheral blood as a predictor of sensorineural hearing loss (SNHL), with some published studies (but not others) supporting this hypothesis [29,30]. Also, weak evidence showed antiviral treatment prevented further deterioration and produced improvement in infants with late-onset hearing loss [31,32]. More high-quality evidence is required.

Conclusion

Our case emphasizes that non-primary maternal infection can also ends up with symptomatic congenital infection that early administration of antiviral treatment is required. Awareness of the disease is essential for early diagnosis and ongoing efforts are aimed at providing evidence to support a decision-making process in perinatal care of these population. In the future, it is also important to clarify whom to test for cytomegalovirus infection and who will benefit from antivirus treatment.

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