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Congenital cytomegalovirus infection in the absence of maternal CMV-IgM antibodies: a case report

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INTRODUCTION

Congenital CMV infection is the most frequently reported viral infection in newborn infants. The prevalence of this infection is estimated between 0.3% and 2.2% of live births[1]. Congenital CMV infection contributes to thousands of children each year being born with or developing permanent disability such as hearing loss, blindness, cerebral palsy and cognitive impairment. In Italy the incidence is between 0.57% and 1% of live births[2]. Maternal infections during pregnancy rarely, if ever, result in a clinically identifiable infection, and exposure to CMV occurs repeatedly in pregnant women. There are well-described exposure risks to CMV that include exposure to young children, sexual activity and living in crowded environments. CMV infection in pregnant women can occur by primary or non-primary infection[3]. Non-primary infection can occur after reactivation of the latent endogenous CMV strain or by reinfection with a different exogenous viral strain. The risk of transmission to the fetus and the severity of the disease depend on two conditions: the maternal serological status and the trimester in which CMV infection occurs[4]. The risk of transmission to the fetus during a primary infection is approximately between 14.2% and 52.4%; for non-primary infection the risk is between 1% and 2.2%[1]. Transmission rate is higher in the third trimester; however, the most significant neonatal sequelae occur when transmission takes place in the first trimester. Up to 10% of newborn with congenital CMV infection are symptomatic at birth. Symptoms range from systemic disease to exclusive central nervous system (CNS) involvement. Forty to sixty percent of symptomatic newborns may develop long-term sequelae, including sensorineural hearing loss, chorioretinitis and cognitive impairment[5-7].

CASE REPORT

A full term male newborn was admitted to a tertiary care NICU because of prenatal ultrasound finding (24 weeks GA) of hyperechogenic spots in basal ganglia and white matter. Maternal anamnestic data reported flu-like symptoms during 1st trimester. Maternal serological tests performed during her previous pregnancy showed seropositivity for CMV. Serological screening for CMV performed during the first trimester showed negative IgM- and positive IgG-CMV antibodies, confirming a past infection. In order to exclude vertical infections, other maternal serological tests were performed, showing seronegativity for *Toxoplasmosis*, *Rubella*, *Zyka virus*, *Chikungunya virus*, *Dengue virus* and absence of IgM antibodies for *Parvovirus B19*, *Herpes virus* and *Cytomegalovirus*. In particular, CMV antibodies profile characterized by IgM negativity and IgG positivity remained unchanged at 22, 26 and 30 weeks of gestation. The fetal MRI performed at 32 weeks of GA showed

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microcephaly, cerebral atrophy, cortical and subcortical calcifications and cerebellar hypoplasia. The baby was born by elective C-section at 38 weeks of gestation, with a birthweight of 3265 g (55°P), a length of 49 cm (49°P) and a head circumference of 32.5 cm (8°P)[8]. The Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Prenatal findings were confirmed by cranial ultrasound, CT scan and MRI performed in the first week of life (Figure 1). Auditory brainstem response (ABR) resulted abnormal in the left ear. Second level metabolic screening tests resulted negative, as well as serological tests for *EBV*, *Parvovirus* B19, *HHV6*, and *HSV1* and *2*. Despite maternal serological pattern, the newborn underwent a full examination for congenital CMV infection. CMV virus was detected by polymerase chain reaction (PCR) test in urine and blood samples (11.5 x 105 copies/ml and 35.5 x 103 copies/ml, respectively). Orally Valganciclovir was started on DOL 35, at 6 mg/kg/dose every 12 hours but was withdrawn after 12 days because of leucopenia. Therapy was resumed 2 weeks later and continued for 5 months. At 2 years of age the neurological follow up showed microcephaly, monolateral hearing loss, cognitive impairment and epilepsy treated with clonazepam and levetiracetam.

DISCUSSION

Primary CMV infection during pregnancy occurs in 1 to 4% of previously seronegative women[9]. The transmission rate of CMV to the fetus following maternal primary infection during pregnancy has been reported to range between 14.2 and 52.4%, with the most studies reporting rates of around 30%[10]. In contrast, the risk and the rate of intrauterine transmission following non-primary maternal infection range between 0.15% to 2%. Importantly, maternal primary and non-primary infections are rarely associated with any clinical symptoms. Acute infection is usually asymptomatic, sometimes women may show flu-like symptoms. Historically, pre-existing maternal immunity was known to reduce the probability of symptomatic congenital CMV infection and the number and severity of *sequelae*. In recent years, however, increasing evidence suggests that non-primary infection may be a significant cause of severe congenital CMV disease[11-14].

The gold standard of serological diagnosis of maternal CMV infection during pregnancy is maternal seroconversion or the presence of serum anti-CMV specific IgM combined with low avidity anti-CMV IgG avidity[10]. However, both American College of Obstetricians and Gynecologist (ACOG) and Center for Disease Control and Prevention (CDC) do not recommend routine screening for CMV during pregnancy because there is neither vaccine nor effective treatment available[15,16]. Furthermore, it is difficult to discriminate primary from recurrent infection on the basis of maternal IgM antibody screening: specific IgM anti-CMV antibodies may be produced during both primary and secondary infections, an elevated IgM titer may persist for months after acute infection and could be frequently falsely positive because of cross-reaction with other viral infections or in autoimmune disease[9]. The anti-CMV IgG avidity test is currently the most reliable commercial procedure to identify primary infection in pregnant women. Antibody avidity indicates the strength of a multivalent antibody to bind a multivalent antigen. During the first weeks following primary infection, IgG antibodies show a low avidity for the antigen, but they progressively and slowly mature, acquiring a moderate and then a high avidity. IgG avidity test may be very useful in the diagnostic process: combination of elevated specific IgM-CMV and elevated specific IgG-CMV antibodies with low avidity suggest a recent CMV infection. Low avidity CMV-IgG usually last for approximately 16-18 weeks after the onset of CMV infection. Negative IgM-CMV antibodies combined with positive IgG-CMV antibodies with high avidity index during the first 12-16 weeks of gestation could be considered a good indication of past infection[10].

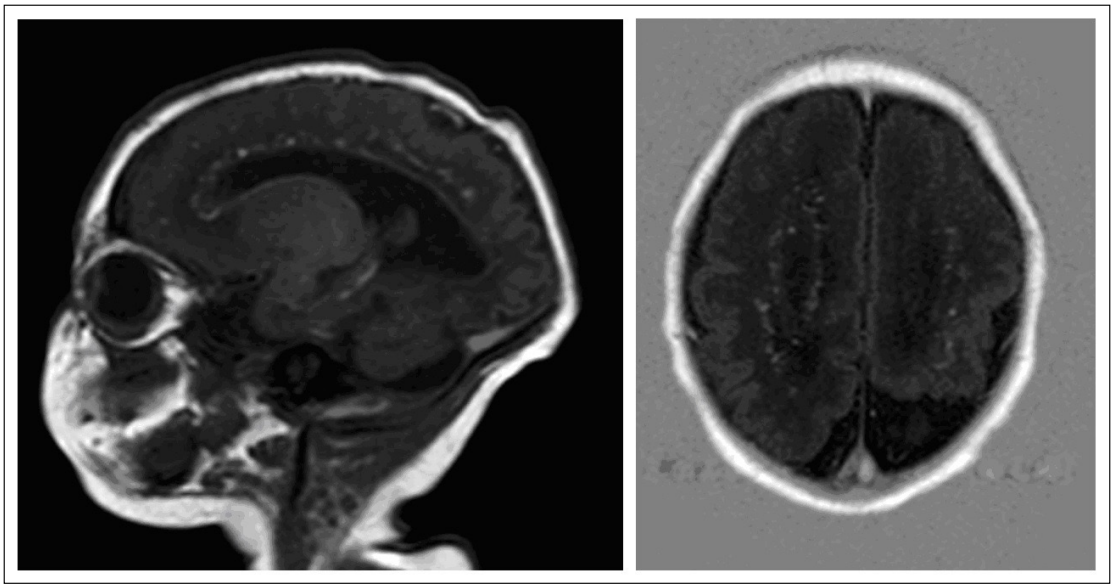

Figure 1. Cranial MRI scan showing cortical and subcortical calcification, venriculomegaly, increased cisterna magna, reduced cerebral convolution and diffuse hyperechoic spots.

In our case, despite fetal US and MRI findings, suggestive of congenital CMV infection occurring in the first trimester of pregnancy, maternal seroconversion or positive CMV-IgM antibodies were never detected. As far as we know there is only one similar case reported in literature. Gunkel et al[17] described the case of a female infant, diagnosed with congenital CMV infection (urine CMV PCR positive), born to a mother seropositive for a past CMV infection both in first trimester and at 22+2 weeks of gestation. It is known that presence of specific IgM is highly variable and sometimes IgM are not detected by routine laboratory tests. According to the recent SIN (Italian Society of Neonatology) recommendations, a serological test resulting in positive IgG anti-CMV and negative IgM anti-CMV antibodies during the first trimester of pregnancy is sufficient to describe a previous infection, and there is no need to do additional tests[2]. In a recent paper Wood et al[9] underline that negative IgM anti-CMV antibodies titer combined with a positive specific IgG anti-CMV titer rules out the possibility of a primary infection, even if a low risk for congenital CMV infection persists[9]. Additionally, increasing evidence shows that the risk of symptomatic infection, especially that resulting in hearing loss, is similar after maternal primary and non-primary CMV infection. Therefore, amniocentesis with polymerase chain reaction (PCR) test should be considered in case of CMV-related findings on ultrasound examinations[14].

CONCLUSIONS

Our case report is remarkable because it shows a serious clinical presentation in a non-primary congenital CMV infection. Furthermore, IgM anti-CMV antibodies remained negative during all pregnancy despite the occurrence of a non-primary maternal CMV infection. In conclusion, non-primay infection cannot be excluded if US findings are characteristic, even if the maternal serology, that stands for past infection, remains unchanged. Therefore, multiple diagnostic steps should be carried out to diagnose fetal infection both during pregnancy and in the neonatal period. In order to confirm fetal infection amniocentesis or fetal blood samples should be considered. In the neonatal period testing for congenital CMV should be performed using real-time PCR of urine obtained within 14-21 days of birth.

Informed Consent:

The informed consent was obtained by the parents of the baby before the study.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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