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Congenital cytomegalovirus infection after maternal persistent immunoglobulin-M antibodies against cytomegalovirus prior to conception

Abstract: We describe a case of congenital cytomegalovirus (CMV) infection transmitted by an immunocompetent woman infected before conception with continuous hyper CMV-immunoglobulin M (IgM). A 33-year-old woman whose CMV-IgM levels were stable more than 8 months before conception was referred at 35 gestational weeks due to fetal unilateral cerebral ventriculomegaly. The maternal serum CMV-IgG was 61.7 U/mL, and the CMV-IgM was 3.89 U/mL. An infant girl weighing 2297 g was delivered transvaginally. The neonate was found to have congenital CMV infection. After delivery, the high maternal CMV-IgM level has continued for more than 2 years. In conclusion, although continuous hyper CMV-IgM is rare, the infants of infected women may develop congenital infection. It is our hope that the information provided in the present case will further aid clinicians in counseling patients who find themselves in this situation.

Keywords: Cytomegalovirus infection; feto-maternal infection; preconceptional infection.

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Introduction

Cytomegalovirus (CMV) is the common cause of feto-maternal infection, and in a meta-analysis study, the birth prevalence of congenital hyper CMV infection was reported to be 0.64% (95% confidence interval 0.60–0.69), with a rate of symptomatic infections at birth of 0.07% [3]. The clinical findings of congenital CMV infection may vary from a congenital syndrome with microcephaly, ventriculomegaly, hepatosplenomegaly, elevated liver enzymes, low platelet counts, and CMV retinitis, to a symptomatic course. Most congenitally infected infants are apparently normal at birth; however, long-term sequelae, most commonly deafness, mental retardation, and neuromuscular defects, occur in up to 40% of cases. The symptoms of congenital CMV infection are worse in cases of primary infection than in cases of recurrent infection [8].

CMV-Immunoglobulin M (IgM) can identify different clinical situations, including the acute phase of a primary infection, the convalescent phase of a primary infection, and the persistence of CMV-IgM.

There is little information about congenital infection after maternal persistent CMV-IgM. We present a case of congenital infection transmitted by an immunocompetent woman infected before conception with continuous hyper CMV-IgM.

Case report

The patient was a 33-year-old primigravida. Her clinical and family histories were non-contributory. She had a history of fever and was referred to a hospital. She had painless cervical lymph nodes. She stated that lymph nodes had appeared accompanied by slight fever and tiredness. She was diagnosed as having primary CMV infection based on a CMV-IgG level of 18.3 U/mL (cut-off value, 2.0) and a CMV-IgM level of 4.68 U/mL (cut-off value, 0.80). CMV-IgM and CMV-IgG were detected using enzyme-linked immunosorbent assay. Antibodies to Epstein-Barr virus were negative. Five days after onset, her symptoms disappeared. She had been followed up serologically every 6 months (Figure 1). She was suspected as having persistent CMV-IgM.

Nine months afterwards, she became pregnant. During the pregnancy, she was not aware of any symptoms. At 35 gestational weeks, she was referred to our hospital due to fetal cerebral ventriculomegaly. Ultrasonographic findings showed the left cerebral ventriculomegaly

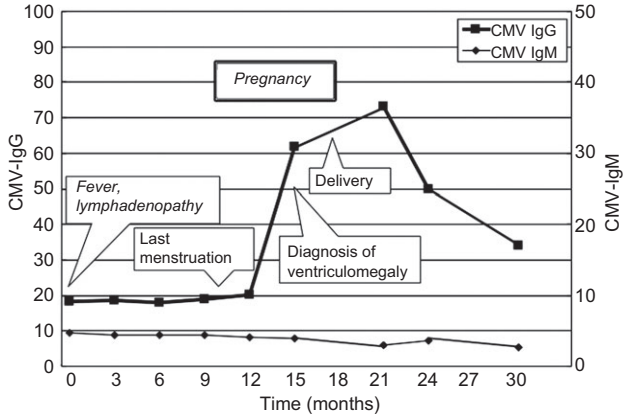

Figure 1 Maternal serum CMV-IgG and CMV-IgM levels before and during pregnancy. All analyses were performed at the same laboratory (SRL Analysis Center for Medical Science, Japan) by ELISA. All measurements are shown as "arbitrary units per milliliter".

with a corresponding cerebral atrial width [7] of 18 mm (Figure 2); the estimated fetal weight was around the 10th percentile for gestational age; no other fetal abnormalities were evident. The maternal CMV-IgG and CMV-IgM levels were 61.7 and 3.89 U/mL, respectively; however, the serum CMV-DNA (polymerase chain reaction) was negative. Laboratory tests were performed to rule out other causes of this condition. Antinuclear antibodies, anti-DNA antibodies, antiphospholipid antibodies, and TORCH infections [toxoplasmosis, other (coxsackievirus, syphilis, varicella-roster virus, HIV, parvovirus B19), rubella, cytomegalovirus, and herpes] were negative. Although we suspected congenital infection based on the fetal findings and maternal serology, we thought that it was too late to perform CMV isolation by amniocentesis for prenatal diagnosis.

At 39 gestational weeks, she had an uncomplicated vaginal delivery. The infant girl was born weighing 2297 g (fifth percentile for gestational age for Japanese neonates). Serological examination of the umbilical blood showed the following results: CMV-IgG, 813 U/mL; CMV-IgM, 8.17 U/mL; and CMV-antigenemia, positive.

The infant was admitted to the neonatal intensive care unit. On admission, laboratory findings showed a slightly low platelet count (132,000/μL) and a mild elevation of aspartate aminotransferase (48 U/L). Virological tests showed the following results: CMV-IgG, 195 U/mL; CMV-IgM, 7.65 U/mL; CMV-antigenemia, positive. High cerebrospinal fluid levels of IgG (28.7 mg/dL) and IgM (0.9 mg/dL) were detected. Magnetic resonance imaging showed enlargement of the left cerebral ventricle due to destruction of the cerebral cortex and edematous change in the bilateral periventricular area (Figure 3). Electroencephalography showed a normal pattern, but automated auditory brainstem response revealed that both ears had a sensory deafness pattern. Examination results for other possible infections, such as TORCH infection, hepatitis viruses, HIV, and parvovirus B19, were negative. The neonate was diagnosed as having congenital CMV infection.

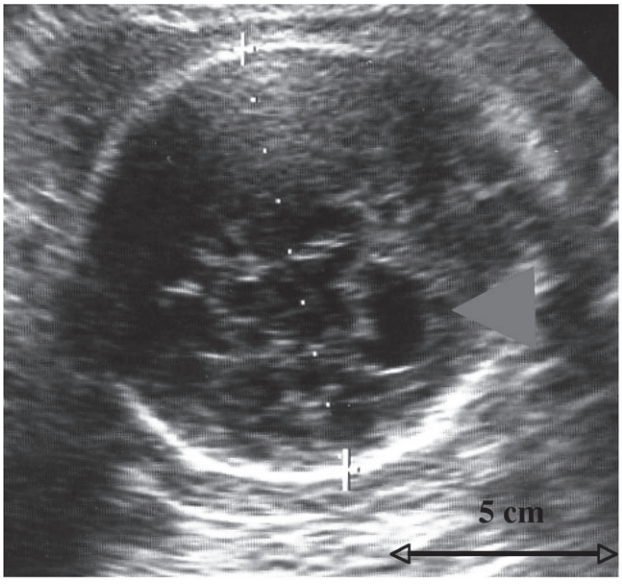

Figure 2 Fetal ultrasonographic image at 35 weeks' gestation. Ultrasonographic evaluation shows enlargement of the fetal cerebral ventricle at the left posterior horn. The cerebral atrial width is 18 mm (arrow).

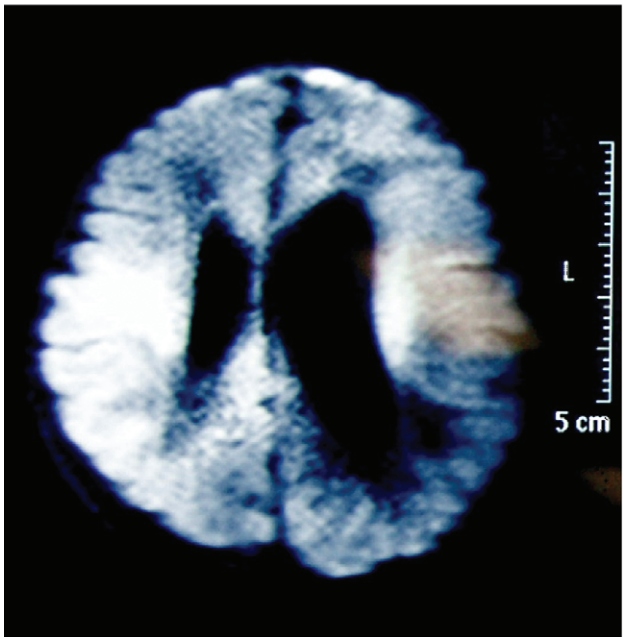

Figure 3 Neonatal magnetic resonance images (MRI). T2-weighted fluid-attenuated inversion recovery (FLAIR) contrast image of the neonatal cross-sectional view on admission.

The neonate was treated with intravenous ganciclovir and immune globulin therapy. On the 74th day of life, the neonate was discharged. The CMV-IgG and CMV-IgM levels were 36.3 and 6.80 U/mL, respectively. The CMV-antigenemia had changed to negative.

After delivery, the high maternal CMV-IgM level has persisted for more than 2 years.

Discussion

CMV-IgM can be identified in different clinical situations, including the acute phase of a primary infection, the convalescent phase of a primary infection, or the persistence of CMV-IgM. The diagnosis of a primary infection is based on the detection of CMV-IgM antibodies, a four-fold or greater rise in the titer of CMV-IgG antibodies, or seroconversion [1], whereas CMV-IgM is absent in recurrent infection. CMV-IgM antibodies may sometimes persist for long periods following primary infection; they may also be produced following reinfection or reactivation. Revello and Gerna [8] defined persistent CMV-IgM as the detection of stable levels of CMV-IgM for longer than 3 months.

In the present case, CMV-IgM was detected for more than 2 years before, during, and after pregnancy. Since the patient did not have any symptoms of CMV infection before and during pregnancy, and her CMV-IgM level was stable, recurrent infection was excluded. In addition, distinguishing between persistent IgM and persistent infection is difficult. Non-specific positive CMV-IgM antibodies may be due to cross-reaction with rheumatoid factor, auto-antibodies, IgM to other herpesviruses, and polyclonal B-cell activation following CMV infection. However, these possibilities were serologically ruled out in our case. Moreover, the detection of CMV-IgM antibodies was performed in the same laboratory. CMV isolation could not rule out the possibility of reactivation of persistent CMV-IgM or persistent CMV infection. Furthermore, because the CMV-IgG levels were stable, a long period of time must have passed since the onset of the infection.

The first serological test results were positive for CMV-specific IgG and IgM. The second and third serological test results showed identical results for CMV-IgG and a slight fall in CMV-IgM level. The compared immunological profile of these samples also confirmed the stability of the CMV-IgG antibody titer. This stability showed that seroconversion had occurred at least 1 month before the first sample was taken [8]. We concluded that the pregnant woman had thus been infected before conception.

Some authors suggested that the CMV-IgG avidity assay might help distinguish primary from recurrent infection and/or exclude the risk of congenital CMV infection [2]; however, it was not used in the present case. It has been suggested that symptomatic congenital infection is rare in infants of women with preconceptional immunity. Boppana et al. [1] suggested that, among women with preexisting immunity against CMV, intrauterine transmission of CMV to their infants occurs most often in those who had acquired a different strain of CMV between pregnancies. In our case, the patient may have been infected with different strains. The study technique of Boppana et al. [1] for detecting antiviral antibodies may help to address persistent infection vs. new infection with new strain.

Both prenatal and postnatal therapies are considered for the treatment of congenital infection [1]. In our case, although congenital CMV infection was suspected based on the fetal findings and maternal serology, because the time of diagnosis was near-term, prenatal final diagnosis and therapy were not performed. After delivery, the infant was treated with intravenous ganciclovir and immune globulin combination therapy [4]. However, the ventriculomegaly worsened, probably because irreversible damage had already occurred during the prenatal period. With respect to intrauterine therapy, recent studies have suggested that administration of immune globulin to pregnant woman [6] is safe for the infected fetus [5] and mitigates the long-term sequelae. In our case, if the time of diagnosis had been earlier and intrauterine treatment had been given, the outcome might have been improved.

There is little information about how long conception should be delayed following CMV infection. The risk of vertical transmission of human CMV was investigated in 14 women who had primary CMV infection 2–18 weeks before their last menstrual period. One (8.3%) of 12 newborns examined at birth was found to be subclinically infected [9]. Moreover, Revello and Gerna [8] suggested that at least 6 months should elapse prior to initiation of pregnancy, because it has been shown that about 20% of immunocompetent subjects with documented primary infection are still CMV-DNAemia positive 6 months after onset. Although our patient had waited 9 months between infection and conception, her infant developed congenital infection. This finding suggests that a longer interval between infection and conception is needed to avoid congenital infection.

In conclusion, although many authors suggest that maternal serological screening is not recommended [8], in women who develop CMV infection before conception, serologic follow-up is necessary before and during

pregnancy. Moreover, CMV-IgG avidity or yet-to-be – found prognostic markers for transmission of CMV infection to the fetus may be useful for diagnosis and counseling in the future. It is our hope that the information provided in the present case will further aid perinatal doctors in counseling patients who find themselves in this situation.

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