Symptomatic congenital cytomegalovirus infection in two consecutive sisters

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Abstract
The occurrence of symptomatic congenital cytomegalovirus (CMV) infection in two consecutive sisters is reported. The first sibling showed hepatosplenomegaly with slight hyperbilirubinaemia and abnormal liver function tests, right inguinal hernia, and peripheral lymphoedema. Her sister, the product of an uneventful pregnancy showing no signs of CMV reactivation, had life threatening CMV disease, including microcephaly, hepatitis with high serum bilirubin concentrations, and thrombocytopenic purpura.

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Congenital cytomegalovirus (CMV) infection has been recognised as an increasingly grave health problem in all countries, showing widely variable rates of prevalence. More than 10% of CMV infected infants either die early in life or sustain debilitating neurological and/or perceptual organ damage. Although pre-existing maternal antibodies are generally protective, transmission of CMV during pregnancy may follow recurrent infections, occasionally resulting in damage to the fetus. The occurrence of congenital CMV infection in two siblings has been described but it was never symptomatic in both.

We report two consecutive sisters in whom congenital CMV infection was symptomatic.

Case reports
SIBLING 1
In May 1986, after a 39 week pregnancy, during the fifth month of which fever (38-5°C) and high levels of CMV specific IgG antibodies (IgM negative culture not done) occurred, a 26 year old woman delivered a girl with jaundice, hepatosplenomegaly, right inguinal hernia, and oedema of both feet. Abnormal laboratory findings were: platelet count 89×10⁹/l, serum albumin 29 g/l, and concentrations of the serum total (99 µmol/l) and conjugated (55 µmol/l) bilirubin, aspartate aminotransferase (AST) 124 U/l (normal values 5–40 U/l), alanine aminotransferase (ALT) 86 U/l (0–40 U/l), γ-glutamyltransferase (γGT) 236 U/l (7–47 U/l), alkaline phosphatase (ALP) 1007 U/l (245–775 U/l), and lactate dehydrogenase (LDH) 674 U/l (120 to 230 U/l) values. No abnormal results were shown by other examinations, including sex chromatin studies and cranial and abdominal computed tomograms. A liver biopsy specimen showed slight steatosis. CMV infection was shown by viral isolation from urine and saliva and high levels of IgM and IgA antibodies were detected by enzyme immunoassay. The infant's complement fixing titre was 1:32 (the same as her mother, who was negative to culture and IgM and IgA detection). Albumin concentrations returned to normal within a few days concomitantly with frusemide treatment, and jaundice disappeared after about one month. Subsequent virological investigations showed intermittent urine and salivary CMV excretion together with persistently high levels of CMV specific IgA antibodies.

SIBLING 2
Three years after her first delivery the mother had a second pregnancy, and she was kept under observation with approximately monthly examinations of urine and serum samples for CMV infection. No complications occurred and there was no positive CMV culture, no CMV-DNA detection by polymerase chain reaction in urine and serum or CMV specific IgM and IgA antibodies, and no significant increase in IgG concentrations. However, after 39 weeks and an uneventful delivery, the woman gave birth to a girl weighing 2640 g and showing microcephaly (head circumference 30.8 cm, <5th centile), jaundice, hepatosplenomegaly, and purpura. Laboratory examinations showed a serum total bilirubin concentration of 320 µmol/l (conjugated 139 µmol/l), AST 507 U/l, ALT 387 U/l, γGT 89 U/l, ALP 234 U/l, and platelet count 26×10⁹/l.

No periventricular calcifications were shown by cranial radiography and computed tomography. Virological examinations revealed positive CMV culture from urine, high concentrations of CMV specific IgM, and a complement fixing titre >1:128. The mother continued to show negative culture and IgM or IgA antibody detection; her complement fixing titre was the same shown during pregnancy (1:32). After an increase of the infant's bilirubin concentration to 542 µmol/l (conjugated 233 µmol/l), exsanguinotransfusion was carried out. Consequently, her bilirubin concentrations progressively decreased; she also showed neurological improvement together with disappearance of microcephaly (at 3 months the head circumference was 38 cm, corresponding to the 10th centile). Virological follow up showed, as in the older sister, intermittent CMV excretion and a stable complement fixing titre of 1:32.

Discussion
The occurrence of congenital CMV infection in two siblings, born within one to three years, has been previously reported. Embil et al first
Nigro, Clerico, Mondaini described two consecutive children where one had disseminated CMV infection and survived only one month but the second was asymptomatic, although showing viraemia and viruria. Other reports on consecutive congenital CMV infection in siblings, the second of whom was otherwise normal, have been published. Therefore, to our knowledge, this is the first report on two consecutive siblings where the congenital CMV infection was symptomatic in them both.

Our report further shows that, for reasons still unexplained, the presence of CMV specific maternal antibody cannot provide sufficient protection against CMV fetal involvement. Several technical procedures have been proposed for the diagnosis of fetal CMV infection, mainly including culture and detection of CMV-DNA in the amniotic fluid. However, these invasive procedures are suggested when the maternal CMV infection is diagnosed in time for termination of pregnancy.

In our first case, high CMV specific IgG titres were detected during the fifth month of pregnancy, concomitantly with a febrile episode, but no CMV specific IgM antibodies or ultrasonography abnormalities were shown. Subsequently, monitoring of CMV infection by routine examinations of serum and urine was carried out during the second pregnancy, but recurrence of the CMV infection was not seen. As no complications occurred, amniocentesis was not carried out. Therefore, methods more sensitive than culture and detection of CMV-DNA or CMV specific antibodies may be necessary for showing recurrent CMV infection in pregnancy.

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