MOTHERISK UPDATE

Benjamin Bar-Oz, MD Matitahu Berkovitch, MD Lee Ford-Jones, MD Gideon Koren, MD, FRCPC

Congenital cytomegalovirus infection

Is there a breakthrough?

abstract

QUESTION My 26-year-old patient is planning her first pregnancy in the coming month. She works in a day-care centre. Recently, two cases of cytomegalovirus (CMV) infection were diagnosed in her class. What tests should she have before and during the pregnancy, and how should I care for her?

ANSWER Cytomegalovirus infection, the most common congenital viral infection in humans, carries high risk of long-term morbidity and mortality. Seronegative mothers of children in day-care centres are at as high risk of acquiring the infection as day-care workers themselves. The immune status of at-risk patients should be evaluated as pregnancy progresses. Evidence of fetal infection does not necessarily mean fetal disease or damage. With a primary-infected fetus, termination of pregnancy might be discussed with the parents.

résumé

QUESTION Une de mes patientes âgée de 26 ans envisage devenir enceinte le mois prochain. Elle travaille dans une garderie où deux cas d'infection au cytomégalovirus (CMV) ont récemment été diagnostiqués. Quelles épreuves cette patiente devrait-elle subir avant et pendant la grossesse et quels soins devrais-je lui prodiguer?

RÉPONSE L'infection au cytomégalovirus, l'infection virale congénitale la plus courante chez l'humain, entraîne un risque élevé de morbidité à long terme et de mortalité. Les mères séronégatives d'enfants en garderie sont aussi susceptibles que les employés eux-mêmes de contracter l'infection. Le statut immunitaire des patientes à risque élevé devrait être évalué à mesure que progresse la grossesse. La présence d'une infection fœtale ne signifie pas nécessairement une maladie ou des dommages chez le fœtus. Il y aurait lieu de discuter avec les parents de la possibilité de mettre un terme à la grossesse dans le cas d'un fœtus présentant une infection endogène.

Cytomegalovirus, a β-herpes virus with a double-strand DNA, is a common virus that is transmitted both horizontally (direct person-to-person contact through virus-containing secretions) and vertically (mother-to-infant before, during, and after birth). Infection is usually seen in the perinatal period and during childhood. The spectrum of CMV runs from the most common asymptomatic infection to hepatosplenomegaly and an infectious mononucleosis–like syndrome beyond the neonatal period that sometimes includes a devastating congenital infection.[1,2] Congenital CMV occurs in approximately 1% of all live births in the United States and is considered the most common congenital viral infection humans get.[3-6]

Clinical presentation

About 10% of congenitally infected newborns are symptomatic at birth, and about half of these are small for gestational age. Most symptomatic newborns have multiorgan involvement and neonatal jaundice, purpura, hepatosplenomegaly, transient ascites, pneumonitis, hypotonia, hypertonia, feeding problems, microcephaly, brain damage, intracerebral calcifications, sensorineural deafness, optic atrophy, microphthalmia, and chorioretinitis. Reported mortality is about 30%.

Many of the surviving babies develop long-term sequelae including hearing loss (55%), mental retardation (50%), cerebral palsy (49%), seizures (15%), and

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website (www.cfpc.ca). Some articles are published in *The Motherisk Newsletter* and on the Motherisk website (www.motherisk.org) also.

Motherisk questions are prepared by the **Motherisk Team** *at the Hospital for Sick Children in Toronto.* **Drs Bar-Oz, Berkovitch,** *and* **Ford-Jones** *are members and* **Dr Koren** *is Director of the Motherisk Team.*

visual impairment (15%). The best predictor of abnormal neurodevelopmental outcome is abnormal neuroimaging results in the neonatal period, such as intracerebral calcifications, ventricular dilation, and white matter and migration abnormalities.[7]

Almost 90% of newborns with congenital CMV infection are asymptomatic at birth. At least 10% to 15% of those are at risk of developing long-term sequelae, such as sensorineural hearing loss (7%), microcephaly (2%), mental retardation (3.7%), and speech and language delay (2%).[8,9] Most infants who acquire neurologic abnormalities due to congenital CMV infection are born to mothers who have a primary infection during pregnancy. Deafness might come on after the neonatal period.[5]

With primary CMV infection, reported transmission rates to a fetus are between 24% and 75%. Transmission of CMV from mother to fetus can occur during all three trimesters of pregnancy, probably with equal frequency.[6] Severe adverse neurologic outcomes seem to be more likely when infection occurs during the first half of pregnancy.[5,6,10-12]

Results of ultrasound examination of the fetus showing oligohydramnios, polyhydramnios, nonimmune hydrops, fetal ascites, echogenic bowel, intrauterine growth restriction, microcephaly, ventriculomegaly or hydrocephalus, or intracranial or intrahepatic calcifications should alert physicians to the possibility of CMV infection in the uterus.[3-6,12,13]

Although maternal antibodies before conception do not prevent transmission of CMV to a fetus, they help prevent serious damage.[14,15] Only infants with primary infection have symptomatic CMV infection at birth (18%); mental retardation, bilateral hearing loss, seizures, and death occurred only among these children. The chance of unilateral sensorineural hearing loss (5%), chorioretinitis (2%), microcephaly (2%), or any CMV-related sequelae (8%) was lower among babies who had recurrent infection.[16]

Diagnostic tests

Maternal disease. In active CMV infection, the virus can be cultured from urine, saliva, cervicovaginal secretions, and amniotic fluid. Indirect hemagglutination assay, immunofluorescence assay, neutralization tests, and complementary fixation and enzyme-linked immunosorbent assay (ELISA) are used to identify maternal CMV infection. Because the above-mentioned assays have low sensitivity and specificity, the best known way to confirm primary CMV infection is to demonstrate seroconversion or a four-fold increase in CMV–immunoglobulin G (IgG) antibody titre.

Fetal infection. Maternal history and ultrasound findings should alert physicians to the possibility of congenital infection. Finding CMV-specific immunoglobulin M (IgM) in cord blood is neither sensitive nor specific for diagnosing fetal CMV infection.[4,17] We now diagnose intrauterine CMV infection by isolating the virus from amniotic fluid[4,18-20] or by detecting CMV DNA in the fluid through polymerase chain reaction (PCR). These methods should generally be attempted only when fetal ultrasound (US) scan results are abnormal.

In a recently published study, Lazzarotto et al proposed a stepwise strategy for managing congenital CMV infection.[21] First, fetuses are screened for infection before 16 weeks' gestational age with serologic assays for detecting CMV-specific IgG and IgM. Second, women with primary or undefined infection are offered amniocentesis for viral culture, qualitative PCR, and US scan. Third, the amount of CMV genome in women with positive results of PCR is quantified. This diagnostic strategy, with a cutoff of 105 genome equivalents per mm of amniotic fluid, has a positive predictive value of 100% and a negative predictive value of 94% for identifying symptomatic infected infants.[21] Predicting fetal infection that will result in disease is notoriously difficult. Most infants have normal results, and delayed damage becomes evident on US scan several weeks after maternal infection.

Congenital infection in newborns. When congenital infection is suspected because of history or clinical manifestations, diagnosis is established by detecting the virus in urine, saliva, or cerebrospinal fluid during the first weeks of life. Beyond this period, perinatal or postnatal acquisition of infection through breast milk or contact with toddlers cannot be excluded.

In most cases, serology is of limited use because it lacks sensitivity and specificity for congenital infection. Using PCR for detecting CMV DNA might give more information about the possibility of congenital CMV infection.

Approach and treatment

Evaluation to determine the extent of visceral and central nervous system (CNS) involvement is mandatory after diagnosis of congenital CMV infection. Evaluation should include complete physical and neurologic examination, computed tomography scanning of the brain, ophthalmologic examination, and hearing assessment by brainstem evoked responses.[6,22]

Laboratory tests should include complete blood count; liver function tests; and CSF evaluation for cell count, protein and glucose levels, and CMV culture.[6] Long-term neurodevelopmental, ophthalmologic, and audiologic follow up is strongly recommended.

The only drug currently available for congenital CMV infection with CNS involvement is ganciclovir.[4-6,23] The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group[23] reported that the overall mortality rate among 42 babies with severe symptomatic congenital CMV and CNS disease who received ganciclovir daily for 6 weeks was 9%. The babies resumed shedding the virus in their urine after cessation of therapy. Improvement or stabilization in hearing occurred in 16% of the babies at 6 months or later. Neurodevelopmental assessment at age 2 revealed no improvement in comparison with an untreated group.[22] Ganciclovir might protect babies with symptomatic congenital CMV infection against hearing deterioration, but it produces neutropenia in most patients during the course of therapy.[23]

Prevention

Women who work in day-care centres and nurseries where annual seroconversion rates range from 12% to 20% should find out their antibody status before conception. Seronegative women should ideally adhere to strict hygiene practices to reduce the risk of acquiring primary CMV.[3] Washing the hands after contact with urine or saliva reduces risk. Identification and follow up of at-risk women at a high-risk pregnancy clinic should be offered.[4-6]

An experimental, live attenuated vaccine has been shown to be safe and effective for patients with renal transplants and for healthy adult volunteers. Its safety and efficacy have not been proven for preventing congenital CMV infection.[5,6] Recombinant CMV vaccines, based on the antigenicity of surface glycoproteins of the virus, are currently in clinical trials.[3-6]

References

1. Committee on Infectious Diseases, American Academy of Pediatrics. Cytomegalovirus infection. In: Pickering LK, editor. *Red book*. 25th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2000. p. 227-30.
2. Hirsch MS. Cytomegalovirus and human herpesvirus types 6, 7, and 8. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JR, Kasper DL, et al, editors. *Harrison's principles of internal medicine*. 14th ed. New York, NY: McGraw-Hill Co; 1998. p. 1092-5.
3. Brown HL, Abernathy MP. Cytomegalovirus infection. *Semin Perinatol* 1998;22(4):260-6.
4. Friedman S, Ford-Jones EL. Congenital cytomegalovirus infection: an update. *Pediatr Child Health* 1999;4(1):35-8.
5. Demmler GJ. Summary of a workshop on surveillance for congenital cytomegalovirus disease. *Rev Infect Dis* 1991;13:315-29.
6. Nelson CT, Demmler GJ. Cytomegalovirus infection in the pregnant mother, fetus, and newborn infant. *Clin Perinatol* 1997;24(1):151-60.
7. Boppana SB, Fowler KB, Vaid Y, Hedlund G, Stagno S, Britt WJ, et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. *Pediatrics* 1997;99(3):409-14.
8. Stagno S. Cytomegalovirus. In: Remington JS, Klein JD, editors. *Infectious diseases of the fetus and newborn infant*. 4th ed. Philadelphia, Pa: WB Saunders; 1995. p. 312-53.
9. Williamson WD, Percy AK, Yow MD, Gerson P, Catlin FI, Koppelman ML, et al. Asymptomatic congenital cytomegalovirus infection. *Am J Dis Child* 1990;144:1365-8.
10. Griffiths PD, Baboonian C. A prospective study of primary cytomegalovirus infection during pregnancy: final report. *Br J Obstet Gynaecol* 1984;91:307-15.
11. Yow MD, Williamson DW, Leeds LJ, Thompson P, Woodward RM, Walmus BF, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. *Am J Obstet Gynecol* 1988;158(5):1189-95.
12. Stagno S, Pass RF, Cloud G, Britt WJ, Henderson RE, Walton PD, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. *JAMA* 1986;256(14):1904-8.
13. Yamashita Y, Iwanaga R, Goto A, Kaneko S, Yamashita F, Waseda N, et al. Congenital cytomegalovirus infection associated with fetal ascites and intrahepatic calcifications. *Acta Paediatr Scand* 1989;78(6):965-7.
14. Stagno S, Reynolds DW, Huang E-S, Thames SD, Smith RJ, Alford CA Jr. Congenital cytomegalovirus infection: occurrence in an immune population. *N Engl J Med* 1977;296:1254-8.
15. Medearis DN. CMV immunity: imperfect but protective. *N Engl J Med* 1982;306:985-6.
16. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992;326:663-7.
17. Demmler GJ. Congenital cytomegalovirus infection and disease. *Adv Pediatr Infect Dis* 1996;11:135-62.
18. Lamy ME, Mulongo KN, Gadisseux JF, Lyon G, Gaudy V, van Lierde M. Prenatal diagnosis of fetal cytomegalovirus infection. *Am J Obstet Gynecol* 1992;166(1 Pt 1):91-4.
19. Revello MG, Baldanti F, Furione M, Sarasini A, Percivalle E, Zavattoni M, et al. Polymerase chain reaction for prenatal diagnosis of congenital human cytomegalovirus infection. *J Med Virol* 1995;47(4):462-6.
20. Fowler SL. A light in the darkness: predicting outcomes for congenital cytomegalovirus infections. *J Pediatr* 2000;137(1):4-6.
21. Lazzarotto T, Varani S, Guerra B, Nicolosi A, Lanari M, Landini MP. Prenatal indicators of congenital cytomegalovirus infection. *J Pediatr* 2000;137(1):90-5.
22. Williamson WD. The longitudinal assessment of congenitally infected infants. *Semin Pediatr Neurol* 1994;1(1):58-62.
23. Whitley RJ, Cloud G, Gruber W, Storch GA, Demmler GJ, Jacobs RF, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis* 1997;175(5):1080-6.

...