American Journal of Obstetrics and Gynecology (2006) **194**, 1532–6

ELSEVIER

American Journal of Obstetrics & Gynecology

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CLINICAL OPINION

Lymphocytic choriomeningitis virus: An emerging obstetric pathogen?

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Received for publication September 29, 2005; revised November 18, 2005; accepted November 28, 2005

KEY WORD
Lymphocytic choriomeningitis virus

A report in May 2005 from the Centers for Disease Control and Prevention describing a cluster of lymphocytic choriomeningitis virus (LCMV) infections among 4 solid organ recipients has increased awareness of and clinical interest in this pathogen. Human infection with LCMV results from direct or indirect contact with rodents. LCMV has particular relevance to obstetrics, as it is likely an under-recognized abortifacient and fetal teratogen. There have been 54 cases of congenital LCMV reported since 1955, with 34 of the cases diagnosed since 1993. Chorioretinitis and hydrocephalus are the predominant characteristics among children diagnosed with congenital LCMV infection. Obstetricians should educate their pregnant patients about the risks of exposure to laboratory, pet, and wild rodents.

In May 2005, the Centers for Disease Control and Prevention reported a cluster of lymphocytic choriomeningitis virus (LCMV) infections among 4 solid organ recipients who received organs from a single apparently asymptomatic donor.[1] All 4 recipients had severe illness develop, and 3 died. Subsequent investigation of the donor's home revealed that a recently acquired pet hamster as well as the family member who cared for the hamster had evidence of LCMV infection. This report, combined with another cluster of solid organ transplant-associated deaths associated with LCMV infection in Wisconsin in 2003,[1] has increased awareness of and clinical interest in this pathogen within the infectious disease and transplant communities. In addition to its pathogenic potential for solid organ transplant recipients, this virus has particular relevance to obstetrics, as it is likely an under-recognized abortifacient and fetal teratogen. Despite the important obstetric implications of this pathogen, many obstetricians remain unaware of the relevance of LCMV infection for the pregnant woman.

The first identified arenavirus, LCMV, was isolated in 1933 and shown to cause aseptic meningitis in humans.[2] The family *Arenaviridae* includes several human pathogens that are found in the Americas, Europe, and West Africa. Each virus is associated with a single rodent species that serves as the natural host, with human infections resulting from direct or indirect rodent contact. Like the other arenaviruses, LCMV is enveloped and has a single-stranded RNA genome. The natural

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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0002-9378/$ - see front matter © 2006 Mosby, Inc. All rights reserved.
doi:10.1016/j.ajog.2005.11.040

rodent host for LCMV is the house mouse (*Mus musculus*), but the virus has also been found in other rodents such as hamsters, rats, and guinea pigs.[3] Mice infected in utero fail to mount an immune response[4] and develop a chronic, asymptomatic infection, carrying high levels of virus that are shed in their urine, feces, nasal secretions, saliva, milk, and semen throughout their lives.[5] Humans can be infected through direct contact with the rodents, contact with material contaminated with rodent excreta, aerosolization of the virus, or through rodent bites.[6,7] Transmission from person to person has not been observed, with the exception of the recently reported transmission via organ transplantation[1] and vertical transmission from mother to fetus. Disease in immunocompetent humans is rarely fatal, though severe meningoencephalitis has been reported. LCMV infection among immunocompetent adults may be asymptomatic or limited to a nonspecific, self-limited viral syndrome (fever, myalgia, headache, nausea, and vomiting) after a 1- to 3-week incubation. Illness can progress to include meningitis and meningoencephalitis; in addition, less common neurologic manifestations such as paralysis and sensorineural hearing loss have been reported. Uncommon non-neurologic manifestations of illness include pancreatitis, orchitis, arthritis, pericarditis, and rash.[8] LCMV was associated with approximately 10% of aseptic meningitis syndromes among patients hospitalized in a Washington, DC hospital between 1941 and 1958 (Table).[9] However, in more recent times, LCMV may be a less frequent cause of meningitis. For example, among 813 cerebrospinal fluid (CSF) samples from patients undergoing a diagnostic lumbar puncture over a 1-year period at 2 Birmingham, AL, hospitals, LCMV was not detected in any samples using a highly sensitive polymerase chain reaction (PCR) assay for LCMV.[10] Recognized outbreaks of LCMV infection have been reported in the United States, France, and Germany[8] and have been associated with exposure to infected laboratory mice or pet hamsters.

Prevalence of LCMV in wild mice in the United States varies with geographic location and has been reported to range between 3% and 20%.[1] Human disease transmission from wild mice is determined by the distribution of the reservoir, ecologic factors that affect their habitats, and by behaviors and practices that expose humans to virus in rodent excreta. Serologic studies in humans in the United States have indicated that the prevalence of LCMV antibodies among humans is approximately 5% and may be decreasing over time.[1,11] Park et al[11] examined 1600 sera from patients admitted to a hospital in Alabama in 1997. The overall prevalence was 3.5%; however, in those younger than 30 years, it was 0.3% compared with 5.4% in those older than 30 years.[11] A higher frequency in women, the elderly, and individuals residing in substandard housing, mobile homes, or inner-city dwellings infested with mice has been described. In Baltimore, 9% of house mice and 4.7% of patients at a sexually transmitted disease clinic had LCMV antibody.[12,13] In a 2003 study from Spain, the corresponding prevalence was 9% in wild rodents and 1.7% in humans.[14] In an urban location in Argentina, the prevalence of LCMV antibodies was 1% to 3.6% between 1998 and 2003 among 2594 humans and 12.9% among house mice.[15] Human infections seem to occur more commonly in the fall and winter months, as rodents move indoors. Although serosurveys have been conducted on wild mice populations, little is known about the prevalence of LCMV among household pet and laboratory rodents.

Although LCMV infection is prevalent among mice, it is not a commonly diagnosed cause of illness in humans and does not appear to cause much symptomatic illness in immunocompetent hosts. However, outbreaks among immunosuppressed transplant recipients serve to remind us that the virus remains present in the household environment, whether because of incursions by wild mice or brought in with a pet rodent. Moreover, prenatal infection with this agent is important because of the impact on the fetus. Early first-trimester illness with LCMV is associated with an increased risk of spontaneous abortion.[7] In addition, infection of the pregnant woman with LCMV has been linked to congenital intrauterine infection characterized by hydrocephalus, macrocephaly or microcephaly, and chorioretinis.[6,16,17] Neonatal meningitis can also occur. Although congenital LCMV was believed to be very rare, reporting of cases has increased dramatically in the last decade. Greater awareness and availability of diagnostic testing may be contributing to this increased recognition. There have been 54 cases of congenital LCMV reported worldwide since 1955, including 2 sets of twins; 34 (>60%) of these have been diagnosed since 1993.[16,18] Twenty-six of the cases (48%) were reported in the United States; the geographic distribution spans the north, south, east, west, and midwest United States. Symptomatic maternal illness has been documented in slightly more than half of the mothers of infected infants[6]; rodent exposure of the pregnant woman was noted in more than a third of the cases. Transplacental infection of the fetus presumably occurs during maternal viremia, primarily during the first and second trimesters.[16] It is unclear whether intrapartum transmission of LCMV may also occur.[7]

Chorioretinitis and hydrocephalus are the predominant characteristics among children diagnosed with congenital LCMV infection. Chorioretinitis was described in 48 of 54 infants and hydrocephalus or periventricular calcifications in 23 of 25 infants in whom neuroimaging studies were obtained.[16,18] Other reported ophthalmologic findings include chorioretinal scars, optic atrophy, nystagmus, esotropia, microphthalmia, and cataracts.[6] Mortality among infants diagnosed with congenital LCMV is approximately 30%.[19] Among survivors of recognized congenital LCMV infection, two thirds have

Table Seroprevalence surveys of LCMV

Description of sample	Number of LCMV antibody positive (%)	Comments
Rodents		
House mice (*Mus musculus*) trapped in urban Baltimore 1984-1987[13]	43/480 (9.0)	
Four species of rodents trapped in urban and rural areas of Madrid[14]	9/100 (9.0)	
Rodents trapped in city in Argentina in 1998-2003[15]	76/1038 (7.3)	LCMV found only in *Mus domesticus* species; 76/588 (12.9%) of *Mus domesticus* were LCMV antibody positive
Adults		
Patients hospitalized with aseptic meningitis syndromes, 1941-1958[9]	72/713 (10)	
Sexually transmitted disease clinic clients in Baltimore 1986-1988[12]	54/1149 (4.7)	Prevalence of antibodies ranged from 3.25% in persons $\leq$20 y to 7.9% for persons $>$40 y
Inpatients and outpatients at the University of Alabama hospitals in 1993-1994[10]	11/272 (4.0)	Cerebrospinal fluid samples collected from patients undergoing diagnostic lumbar puncture: 0/813 were positive by PCR or ELISA (IgM)
Inpatients and outpatients at the University of Alabama hospitals in 1995[11]	56/1600 (3.5%)	Prevalence of antibodies ranged from 0.3% in patients $<$30 y to 5.4% in patients 30 y and older
Adults living in rural and urban areas of Madrid[14]	7/400 (1.7%)	Higher prevalence in rural (2.3%) vs urban (1.1%) population
Adults living in city in Argentina in 1998-2003[15]	85/2594 (3.3)	Higher prevalence in males (4.6%) vs females (2.6%)
Pregnant women		
Pregnant women in Lithuania, 1970-1976[21]	11/1784 (0.6)	
Pregnant women living in city in Argentina 1998-2003[15]	7/432 (1.6)	
Asymptomatic Children		
Newborn infants in Lithuania, 1970-1976[21]	7/833 (0.8)	
Children with congenital hydrocephalus		
Infants $<$1 y in Lithuania, 1970-1976[21]	12/40 (30)	
Children in France[22]	1/34 (2.9)	

ELISA, Enzyme-linked immunosorbent assay.

long-term neurologic abnormalities including microcephaly, mental retardation, seizures, and visual impairment.[19] However, it is possible that previously reported cases are biased toward the more severe end of the spectrum. A recent report of 2 children with evidence of chorioretinitis and presumed congenital LCMV infection without neurologic manifestations support this possibility.[20] Differential diagnosis of congenital LCMV infection includes cytomegalovirus (CMV), toxoplasmosis, rubella, and herpes simplex virus (HSV). Although toxoplasmosis, CMV, and LCMV all present with intracranial calcifications, those related to LCMV and CMV tend to be periventricular in location compared with diffuse intracerebral calcifications in toxoplasmosis.[7] However, in contrast to congenital CMV infection, hearing deficits and hepatosplenomegaly are infrequent with LCMV and were noted in only 4 and 2 neonates, respectively.[18] Unlike congenital rubella, a congenital heart defect was described in only 1 infant with LCMV,[17] and compared with parvovirus B19, profound fetal anemia leading to heart failure and fetal death (nonimmune hydrops fetalis) is not common, also described in only 1 infected infant.[18] However, available information on congenital LCMV infection has been obtained from study of infants ascertained because of suspected congenital LCMV; prospective investigation is necessary to determine the true frequency of clinical manifestations among infants who are congenitally infected.

The true prevalence of congenital LCMV infection is unknown. Sheinbergas[21] reported the results of a serologic survey of 833 normal infants, 110 infants with various neurologic conditions, and 40 infants with hydrocephalus; among these infants the serologic prevalence of antibodies was 0.8%, 2.7%, and 30% respectively. Chastel et al[22] serologically surveyed 452 infants with major medical problems (such as jaundice, hepatosplenomegaly, prematurity, neurologic problems) or congenital malformations and found 1 infant (0.2%) with LCMV. No congenital infections were identified among 288 healthy urban delivering mothers and their children examined serologically in a study from Argentina.[15]

In contrast, Mets et al[17] studied 95 pediatric patients residing in a home for severely mentally retarded persons; they found 2 patients with chorioretinal scars

and high LCMV titers without evidence of *Toxoplasma gondii*, rubella virus, CMV, or HSV infection. They also assessed 14 pediatric patients with chorioretinitis diagnosed during a 36-month period at a pediatric hospital in Chicago and found 4 cases with evidence of prior LCMV infection.[17] These findings lend support to the idea, proposed by Barton and Mets, that congenital LCMV infection might be much more common than recognized. Although chorioretinitis caused by LCMV most commonly involves retinal degeneration and optic disk subatrophy, the overlap of symptoms and ocular findings with congenital CMV and toxoplasmosis makes clinical diagnosis difficult.[19] Given the need for potentially toxic therapeutic agents for toxoplasmosis, specific diagnostic testing to rule out LCMV is advisable.[17]

The laboratory diagnosis of congenital LCMV is made using either an immunofluorescent antibody test or an enzyme immunoassay to detect specific antibody in blood or cerebrospinal fluid.[7] Several authors have noted that the widely available complement fixation test is insensitive and should not be used for diagnosis.[17] A PCR assay has been recently developed[23]; however, virus may not be present in the blood or CSF by the time the affected child is born. In the future, PCR may be used for prenatal diagnosis[18]; however, currently there are no reports of prenatal diagnosis by any method such as PCR of amniotic fluid or periumbilical blood samples or specific findings on ultrasound. In congenital infection, both maternal and infant immunoglobulin G (IgG) are positive, with the infant's IgG titer typically 4-fold higher than the maternal IgG titer. IgM is often negative, likely reflecting acquisition of infection earlier in gestation.[16] Virus isolation is not routinely used for diagnosis. There is currently no specific treatment for LCMV. Ribavirin has been used in some cases given the agent's in vitro inhibitory effect on arenaviruses; however, its efficacy has not been demonstrated in a clinical trial.[16] The use of ribavirin in pregnancy is not generally recommended because animal studies suggest the possibility of teratogenic effects.[24]

There are a number of viral and parasitic infections that can cross the placenta and cause substantial damage to the developing fetus. Most obstetricians are familiar with the teratogenic effects of the TORCH infections (TOxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus). However, LCMV as a cause of birth defects is less well known among obstetricians. Although congenital LCMV infection was first described in 1955,[7] the first cases of congenital infection in the United States were not reported until the 1990s. The true incidence and full clinical spectrum of congenital LCMV infection is still unclear; however, the reported incidence of disease has increased over the past 15 years, rendering it a potentially important emerging pathogen. It also is likely that the reported cases of congenital LCMV represent a substantial underestimate, with many cases going unrecognized or undiagnosed. Therefore, when a fetus has ultrasound evidence of ventriculomegaly or an infant has hydrocephaly or chorioretinitis, the diagnosis of LCMV should be considered. In addition, obstetricians should educate their pregnant patients about the risks of exposure to laboratory, pet, and wild rodents. Pregnant women should be counseled to minimize contact with potentially infectious rodents and their excreta to prevent LCMV infection as well as other potential infectious diseases, in much the same way they are advised to avoid contact with cat excreta to prevent toxoplasmosis infection. Of note, although the mode of exposure is often unknown, there has been at least 1 case of a pregnant women acquiring LCMV from a pet hamster.[25] However, counseling of a woman already exposed to rodents during her pregnancy is challenging. The likelihood that a woman will become infected after exposure is unknown. In addition, the frequency of congenital LCMV infection among infants born to women infected during pregnancy and what proportion of congenitally infected infants will have clinical manifestations are also unknown.

As an underrecognized and underreported viral teratogen, LCMV may represent an important and emerging obstetric pathogen. Obstetricians should familiarize themselves with this virus and counsel their patients to minimize contact with potentially infectious rodents and their excreta. Furthermore, additional studies are needed to define the true incidence of congenital LCMV infection and to better characterize its clinical course.

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