Congenital Lymphocytic Choriomeningitis Virus Infection: Decade of Rediscovery

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Lymphocytic choriomeningitis virus (LCMV) is an underdiagnosed fetal teratogen. This diagnosis should be considered for infants and children with unexplained hydrocephalus, micro- or macrocephaly, intracranial calcifications, chorioretinitis, and nonimmune hydrops. The immunofluorescent antibody test is the only reasonable, commercially available, screening diagnostic tool. The differential diagnosis of congenital LCMV infection includes toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, enteroviruses, human parvovirus B12, and syphilis. The infection has also been misdiagnosed as various neurologic, ophthalmologic, and chromosomal syndromes. Further research, to determine the prevalence of this infection in human and rodent populations, and prospective studies, to delineate the clinical spectrum of congenital infection, are needed. The public and members of the medical profession should be made aware of the hazard that wild, pet, and laboratory rodents pose to pregnant women.

Lymphocytic choriomeningitis virus (LCMV) is an often undiagnosed cause of sporadic or epidemic, acquired or congenital infection in humans. This prototypic member of the Arenaviridae family was first isolated in 1933 by Armstrong and Lillie [1]. The virus was subsequently isolated from samples obtained for culture from patients with aseptic meningitis and was established as a cause of that syndrome [1, 2]. Congenital infection with LCMV was initially recognized in England in 1955 [3], but it was not recognized in the United States until 1992 [4, 5]. Twenty-one infants from 9 states in the United States (in the East, West, Midwest, North, and South) have now had congenital LCMV infection diagnosed [4–9] (G. Istre, S. Feldman, A. Merritt, and V. Hanson, personal communication), for a total of 49 cases reported worldwide [10–14]. Recent identification of 3 fatal arenavirus infections in California has resulted in increased awareness of the pathogenic potential of this family of viruses. Eighteen arenavirus species are, in fact, currently recognized; 6 of these species, including LCMV and the etiologic agents of 5 hemorrhagic fevers, cause human disease. We present this review to aid recognition and stimulate further study as well as to ultimately aid in the treatment and prevention of congenital LCMV infection.

ACQUIRED LCMV INFECTION

Chronically infected mice and hamsters are the primary sources of postnatal LCMV infection in humans. Wild mice (Mus musculus) that are infected in utero while they have maternal lymphocytic choriomeningitis viremia fail to develop an effective immune response and remain asymptomatic. They shed the virus in nasal secretions, saliva, milk, semen, urine, and feces. Hamsters that are infected with LCMV develop viremia and viruria with variable effects on their health. Humans acquire LCMV by inhalation of aerosolized virus or by direct contact with fomites contaminated with infectious virus. Infection is characterized by local replication of virus, followed by dissemination to the reticuloendothelial system and subse-
quent viremia. Human-to-human infection has not been well documented. Asymptomatic or mild acquired LCMV infections occur in approximately one-third of patients. Approximately half of the remaining patients develop CNS disease, predominantly aseptic meningitis or meningoencephalitis. Classic LCMV infection is a biphasic disease with the following initial symptoms: fever, malaise, myalgia, headache, photophobia, nausea, vomiting, sore throat, cough, and adenopathy. Defervescence and abatement of constitutional symptoms ensue, followed by development of CNS disease. Neurologic symptoms, however, may present with no prodrome or may never develop.

Between 1941 and 1958, ∼10% of 1500 hospitalized patients had aseptic meningitis that was ascribed to LCMV [2]. It was the most frequently diagnosed etiology during the winter months, when mice presumably move indoors to seek food and shelter from inclement weather. Transverse myelitis, eighth nerve deafness, Guillain-Barré syndrome, and transient and permanent hydrocephalus have also been reported [15]. Extranuclear disease has included pharyngitis, pneumonia, myocarditis, parotitis, and dermatitis [16]. Although recovery is generally complete, it may require months to achieve. Headache, fatigue, and alopecia have been reported during convalescence. Fatalities are rare.

Laboratory abnormalities that can occur during the initial febrile phase include leukopenia, thrombocytopenia, and mildly elevated levels of liver enzymes. Infiltrates that appear on chest radiographs have occasionally been documented. Although the CSF formula may not be pathognomonic of LCMV infection, significant CSF pleocytosis can occur, which is unusual in patients with other viral infections. WBC counts in the CSF have ranged from <30 cells/mm³ to >8000 cells/mm³; in general, the WBCs are predominantly mononuclear in type. CSF eosinophilia [17] has also been reported. Normal-to-decreased CSF glucose concentrations and slightly to modestly elevated CSF protein concentrations have been noted.

The protean manifestations and nonspecific laboratory abnormalities of acquired LCMV infection confound specific etiologic diagnosis and have led health care workers to confuse it with other infectious and noninfectious entities, including influenza, infectious mononucleosis, enteroviral and mumps meningoencephalitis, mycoplasma pneumonia, and endemic mycoses (e.g., coccidioidomycosis), as well as hyperemesis gravidarum. Ultimately, correct nosologic classification is based on detection of IgM and IgG antibodies for LCMV.

## CONGENITAL LCMV INFECTION

Transplacental infection of the fetus presumably occurs during maternal viremia, although intrapartum acquisition cannot be excluded with certainty in the neonate in the initial case report [3]. This infant, who was born in England 12 days after maternal illness developed, became febrile and lethargic and died at 12 days of age. Additional studies from Germany, Lithuania, and France have documented the association of intrauterine LCMV infection with the occurrence of spontaneous abortion as well as with congenital hydrocephalus and chorioretinitis in live-born infants [12–14]. Since 1993, there have been 6 reports from the United States and 1 each from Germany and France that have confirmed the teratogenicity of LCMV in humans [4–11]. In total, 49 infants have had congenital LCMV infection diagnosed (G. Istre, S. Feldman, A. Merritt, and V. Hanson, reported and personal communication), including 2 sets of twins; 20 infants had such infection diagnosed before 1993, and 29 infants were given the diagnosis after that date. Complete historical, clinical, and laboratory data unfortunately are not available for all infants and their mothers.

Symptomatic maternal illness, which occurs primarily during the first and second trimesters, was documented in 20 (63%) of 32 women. Exposure to rodents was noted for 17 (46%) of 37 women. Domiciles inhabited while the women were pregnant included farmhouses, trailers, inner-city apartments, and private homes.

Chorioretinitis affected 42 (93%) of 45 infants. The detailed findings regarding the eyes of 14 LCMV-infected infants (28 eyes) who have been reported in the literature from the United States are listed in table 1. The most common abnormality was chorioretinal scarring in the periphery (in 20 eyes). Macular chorioretinal scars, which are also seen in patients with congenital cytomegalovirus (CMV) and toxoplasmosis, were the second most prevalent finding (in 10 eyes); in 5 of these eyes, peripheral scarring was also present (figure 1). Bilateral optic atrophy, which was seen in 3 patients in association with extensive chorioretinal scars, may have been secondary to the scarring. Nystagmus was present in 3 patients, but that finding, along with esotropia and exotropia (in 1 patient each), was probably secondary to the loss

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. (%) of eyesa (n = 28)</th>
</tr>
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<tbody>
<tr>
<td>Chorioretinitis, generalized</td>
<td>20 (71)</td>
</tr>
<tr>
<td>Chorioretinal scars/macula</td>
<td>10 (36)</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Esotropia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Microphthalmos</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

a Each eye may have had more than 1 finding; therefore, the total percentage is >100%.

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of vision due to the chorioretinal scarring. Cataract and microphthalmia were seen in the same eye.

Fifteen (38%) of 40 infants had microcephaly at birth, and 10 (34%) of 29 had macrocephaly. Hydrocephalus or intracranial, periventricular calcifications were noted in 17 (89%) of 19 infants for whom imaging studies were performed. Neurologic sequelae, including cerebral palsy, mental retardation, seizures, and decreased visual acuity, were observed in 32 (84%) of 38 surviving infants. Of these infants, 3 had loss of vision without concomitant neurodevelopmental abnormalities. Of interest, auditory deficits were noted in only 2 infants. Systemic manifestations of neonatal infection were infrequent, although information on this subject is incomplete. Hepatosplenomegaly was documented in only 2 infants; one infant had thrombocytopenia and another had hyperbilirubinemia. The preceding data and subsequent tabulations are, however, admittedly biased; they include patients who had been screened for congenital LCMV infection because of macrocephaly or loss of vision associated with chorioretinitis. No prospective investigations are available that allow for complete description of the congenital LCMV syndrome.

The pathogenesis of congenital LCMV infection may involve both T cell– and B cell–mediated injury. Pathologic examination of the brains of 2 congenitally infected infants revealed lymphocytic infiltration, cerebromalacia, neuroanalysis, gliosis, proliferation, and perivascular edema [18]. Histologic examination of the tissues of an infected fetus revealed lymphocytic myocarditis and extramedullary hematopoiesis [10]; immunohistochemical analysis of fetal brain tissue, by use of LCMV-specific antiserum, confirmed LCMV infection. Experimental intracranial infection of adult mice has been associated with localization and replication of virus in cells of the ependyma [19]. The resultant inflammation and necrosis may explain the aqueductal stenosis and hydrocephalus observed in cases of congenital LCMV infection in humans. LCMV-infected neonatal rats have developed retinitis, which may progress after the cessation of viral replication [20]. Although therapy for congenital LCMV infection has not been attempted, ribavirin, which has been employed successfully for management of other arenavirus infections, as well as immunosuppressive agents are worthy of consideration [21].

**DIFFERENTIAL DIAGNOSIS OF CONGENITAL LCMV INFECTION**

The differential diagnosis of congenital LCMV infection includes the infectious agents, which comprise the expanded acronym TORCHES: toxoplasmosis, rubella, CMV, herpes simplex virus, enteroviruses, and syphilis. These organisms, as well as human parvovirus B19, are capable of producing blood-borne infection in pregnant women with teratogenic effects in their developing fetuses. Infants with congenital LCMV infection have also had a variety of neurologic, ophthalmologic, and chromosomal syndromes misdiagnosed. Several patients who were referred to the authors (L. L. B. and M. B. M.) had in fact previously been seen by geneticists, neurologists, and ophthalmologists who were unaware that LCMV was a fetal pathogen.

A number of clinical and laboratory clues may aid in the consideration of LCMV as an etiologic agent in an infant or child who has chorioretinitis, hydrocephalus, and micro- or macrocephaly (table 2). Symptomatic neonatal CMV and enterovirus infections are generally associated with hepatosplenomegaly, which is rarely noted in patients with congenital LCMV infections. Hearing deficits, which are not common in both symptomatic and asymptomatic infants who were infected with CMV, are unusual in infants with congenital LCMV infection. Congenital rubella syndrome, an entity that has decreased in prevalence but that has not been eliminated after the institution of universal immunization, is associated with cataracts, heart disease, and deafness, all of which have been extremely uncommon in patients with congenital LCMV infection. Both congenital rubella syndrome and congenital syphilis are also associated with a salt-and-pepper retinopathy not found in LCMV-infected infants. In addition, the osseous and hepatic abnormalities that are characteristic of congenital syphilis have been virtually absent in infants with congenital LCMV infection. A recent report of the intrauterine death of an LCMV-infected fetus who had congestive heart failure, myocarditis, severe anemia, and hydrocephalus suggests that LCMV, like human parvovirus B19, should be considered a cause of non-immune hydrops fetalis. Congenital toxoplasmosis remains the most problematic differential diagnosis. As is the case in patients with congenital CMV and LCMV infections, chorioretinitis...
Rubella, herpes simplex virus, and enteroviruses, as well as serologic test titers and the absence of cultures that are positive for CMV, is ultimately confirmed by the presence of LCMV.\footnote{Noted in 1 infant; association with congenital lymphocytic choriomeningitis virus was unclear.}

The diagnosis of this infection should be considered for infants and children with unexplained hydrocephaly, micro- or macrocephaly, intracranial calcifications, chorioretinitis, and non-immune hydrops. Further research to determine the prevalence of LCMV infection in human and rodent populations in diverse geographic locations is clearly needed, as are prospective studies to delineate the clinical spectrum of congenital LCMV infection. Increased recreational activities in rural environments, rehabilitation of and habitation in older, rodent-infested domiciles, and acquisition of unscreened rodents are associated with as-yet-undefined risks for LCMV infection in humans\footnote{Educating the public and medical profession about the hazards of wild, pet, and laboratory rodents pose to pregnant women and yet-undefined risks for LCMV infection in humans}. Education of the public and medical profession about the hazards that wild, pet, and laboratory rodents pose to pregnant women remains a priority.

**ACKNOWLEDGMENTS**

We thank the many physicians, including Drs. Laurie Seaver, Suzanne Cassidy, Stephen Chartrand, Gregory Istre, Sandor Feldman, Allen Merritt, and Vaughn Hanson, who referred and informed us of their patients. Dr. C. J. Peters has been an invaluable information resource regarding arenaviruses (LCMV in particular). Drs. Ali Khan, Thomas Ksiazek, and Pierre Rollin of the Centers for Disease Control and Prevention, Atlanta, provided laboratory assistance. Dr. William Holmes, Beatrice Liebesman, and Johanna Grimes have been continuously supportive. Kim Henney aided in manuscript preparation.

**CONCLUSIONS**

In summary, we contend that the evidence supports the hypothesis that LCMV is an underdiagnosed fetal teratogen. Diagnosis of this infection should be considered for infants and children with unexplained hydrocephalus, micro- or macrocephaly, intracranial calcifications, chorioretinitis, and non-immune hydrops. Further research to determine the prevalence of LCMV infection in human and rodent populations in diverse geographic locations is clearly needed, as are prospective studies to delineate the clinical spectrum of congenital LCMV infection. Increased recreational activities in rural environments, rehabilitation of and habitation in older, rodent-infested domiciles, and acquisition of unscreened rodents are associated with as-yet-undefined risks for LCMV infection in humans. Education of the public and medical profession about the hazards that wild, pet, and laboratory rodents pose to pregnant women remains a priority.

**Table 2. Differentiating features of major congenital infections.**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Retinopathy</th>
<th>Hydrocephaly</th>
<th>Micro- or macrocephaly</th>
<th>Intracranial calcifications</th>
<th>Deafness</th>
<th>Hepatosplenomegaly</th>
<th>Nonimmune hydrops</th>
<th>Cardiac malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?\footnote{a}</td>
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<tr>
<td>Toxoplasmosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Rubella</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Cytomegalovirus</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Syphilis</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Human parvovirus B19</td>
<td>+</td>
<td>+</td>
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</tr>
</tbody>
</table>

**NOTE.** Frequency of findings, ± (very rare), + (uncommon), to +++ (most common).

References


