Lymphocytic Choriomeningitis Virus Infection

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Etiology

Lymphocytic choriomeningitis virus (LCMV) is a member of the genus Arenavirus within the family Arenaviridae. These enveloped viruses contain a single stranded, two-segmented RNA genome of negative polarity with ambisense coding strategy. According to their geographical distribution and phylogenetic relationships arenaviruses can be differentiated into the New World, e.g. Junin and Machupo virus, and Old World, e.g. LCMV and Lassa virus. The small (S) RNA segment codes for the nucleocapsid protein in the negative sense and glycoprotein precursor (GPc) in the opposite sense. The large (L) RNA segment encodes the RNA-dependent RNA polymerase (L protein) on one strand and the matrix (Z) protein on the other strand.

Affected species (wildlife, domestic animals, humans)

Wildlife: Rodents are the natural reservoirs of LCMV and the other arenaviruses. The infection of adult immunocompetent mice results in viral clearance within two weeks; only under certain circumstances a persistent infection will be established. Based on their phylogenetic relationship, host association and geographic distribution four genetic lineages I-IV have been defined. Virus lineages I and II have been exclusively found in the house mouse including both subspecies *Mus musculus musculus* and *Mus musculus domesticus*. A lineage IV LCMV strain has been recently detected in the wood mouse *Apodemus sylvaticus* trapped in Spain. In addition to these reservoirs or potential reservoirs several further wild rodent species were found to be susceptible to LCMV infection. Thus LCMV-specific antibodies have been detected in wild rodents of the following murine and cricetine species: Algerian mouse *Mus spretus*, striped field mouse *Apodemus agrarius*,yellow-necked mouse *A. flavicollis*, wood mouse *A. sylvaticus*, eastern broadtoothed field mouse *A. mystacinus*, harvest mouse *Micromys minutus*, sibling vole *Microtus levis* (formerly *M. rossiaemeridionalis*), Robert's snow vole *Chionomys roberti*, bank vole *Myodes glareolus*, and montane water vole *Arvicola scherman*. In addition, monkeys in captivity have been found to be susceptible for LCMV infection.

Domestic, companion and pet animals: Pet hamsters and guinea pigs represent also reservoirs for LCMV. In addition, dogs, rabbits and chicken have been reported to be susceptible for LCMV infection.

Humans: Human LCMV infections have been reported from several European countries including Austria, Bulgaria, France, Germany, Slovakia, Spain and former Yugoslavia, from Japan and the USA. Virus lineages I–III have all been associated with severe human disease.

Epidemiological characteristics and disease course

Rodents as house mouse and hamsters are LCMV reservoirs and shed the virus in saliva, nasal secretions, urine and feces. Newborn mice were found to survive LCMV inoculation and become clinically healthy life-long carriers. LCMV is transferred vertically from one generation to the next via intrauterine infection. Due to the world-wide distribution of the house mouse, *Mus musculus*, LCMV is thought to be also distributed on all continents except Antarctica, with virus lineages I, II, and IV being detected in Europe and lineages I and III in the United States. Humans can acquire LCMV infection during any season, but most LCMV infections occur during the late autumn and early winter months.

Humans typically acquire a postnatal LCMV infection mediated by direct contact with contaminated fomites or by inhalation of virus-contaminated aerosols, but transmission via organ transplantation has been also reported. In addition, a congenital LCMV infection might be caused by a primary LCMV infection during pregnancy and transplacental transmission of the virus during maternal viremia to the fetus. Further, the virus might be transmitted also later during parturition. A horizontal LCMV transmission from human to human has not been reported. The knowledge on the epidemiological situation in the human population is only scarce and based on single case reports. Seroprevalence studies in the human population are very rare. The high prevalence of infected mice and of seropositive postnatal humans suggest that congenital LCMV infection is an underdiagnosed disease and that the virus is responsible for more cases of congenital neurologic and vision dysfunction than has previously been recognized.

Clinical signs

Humans: The clinical manifestations of postnatal LCMV infection are broad but usually mild and self-limited. In about one-third of infected people, the disease is asymptomatic. After an incubation period of 6 to 20 days the infection is typically with initial symptoms including fever, headache, malaise, myalgia, anorexia, nausea, and vomiting. Temporary improvement of these systemic symptoms is often followed by a second phase with central nervous system (CNS) symptoms. These symptoms are typically those of classic aseptic meningitis and include headache, photophobia, fever, vomiting, and nuchal rigidity. Some patients develop not only CNS symptoms, but extraneural disease like pneumonitis, myocarditis, orchitis, parotitis, dermatitis, and pharyngitis. In addition, the CNS disease in some patients may be considerably more severe than just aseptic meningitis. Other CNS effects have included encephalitis, hydrocephalus, transverse myelitis, and Guillain–Barré syndrome. Sometimes the disease course is much more severe, and fatalities from acquired LCMV infection have been reported. Transplant recipients developed severe disease, including encephalopathy, coagulopathy, abdominal pain, thrombocytopenia, fever, leukocytosis, and graft dysfunction. The entire course of acquired LCMV disease is usually 1 to 3 weeks, although the symptoms may last for several months.

For congenital (prenatal) infections the consequences are typically severe. Infection of the human fetus with LCMV can induce spontaneous abortion and fetal death. Among all surviving fetuses, the common signs of congenital LCMV infection are vision impairment because of chorioretinitis and brain dysfunction. Brain function in children with congenital LCMV infection is virtually always adversely affected. However, the impairments and severity vary from case to case. Children with microencephaly and periventricular calcifications virtually always have severe mental retardation, spastic quadriparesis, and epilepsy. In contrast, patients with isolated cerebellar hypoplasia typically have ataxia and mild-to-moderate learning disabilities.

Rodents: Rodents that acquire LCMV transplacentally may be heavily infected with virus, but often remain asymptomatic because the virus is not cytolytic and because congenital infection in rodents provides them with immunologic tolerance for the virus.

Gross lesions

LCMV patients: Congenital LCMV infection often leads to macrocephaly or to microcephaly. Additional pathologic features often observed include periventricular calcifications, cortical dysplasia, focal cerebral destruction, and cerebellar hypoplasia, bilateral chorioretinal scars, mostly in the periphery of the fundus, although the macula may also be involved.

Histological lesions

LCMV is not a cytolytic virus in most cell types, including neurons.

Differential diagnosis

Meningitis: other viruses, e.g. enteroviruses, herpesviruses, Toscana virus, other encephalitis viruses, such as West Nile virus and Japanese encephalitis virus and others.

Symptoms of congenital LCMV infection: other pathogens that can cross the placenta and damage the developing fetus, i.e. “TORCHS” (*Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus, and syphilis), congenital infections by Varicella zoster virus, parechovirus, and human immunodeficiency virus, and noninfectious entities. Chromosomal abnormalities are prominent causes of microencephaly.

Criteria for diagnosis

Humans: Virus isolation in Vero, L929 or BHK-21 cells remains the method of reference and should be attempted whenever possible. Serological detection of LCMV-specific IgM antibodies or molecular detection of LCMV in serum and liquor is needed for diagnosis of acute infections.

Reservoirs: Serological detection of LCMV-specific IgM and IgG antibodies or molecular detection of LCMV. The presence of LCMV-specific antibodies does not preclude virus isolation.

Recommended diagnostic method(s) and preferred samples (incl. recommended amount and appropriate storage)

At present time the protocols for detection of LCMV by molecular and serological methods must be improved.

(a) *Serological detection of LCMV-specific antibodies*

- Immunofluorescence assay using LCMV-infected cells for detection of LCMV-specific IgM and IgG antibodies
- ELISA: for LCMV-specific IgM and IgG antibodies

→ Samples: serum and cerebrospinal fluid (CSF).

(b) *Molecular detection of LCMV*

- reverse transcription-PCR targeting a conserved region within the polymerase-encoding sequence of the L RNA segment of arenaviruses.
- real-time RT-PCR: LCMV-specific real-time RT-PCR assay, based on detection of nucleocapsid protein-encoding sequences

→ Samples: serum and cerebrospinal fluid (CSF).

APHAEA protocol (for harmonization at large scale)

ELISA or IFA for antibody detection in reservoirs and spillover-infected sentinels.

Laboratories that can be contacted for diagnostic support

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Recommended literature

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European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) http://www.enivd.de/index.htm