

Lymphocytic Choriomeningitis

*Armstrong's Disease,
Callitrichid Hepatitis*

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• Diagnosis of Animal Disease and
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• Day-One Veterinary Competencies
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Importance

Lymphocytic choriomeningitis is a zoonotic disease caused by a virus normally carried in rodents. Although rodents can become ill or suffer other adverse effects, such as a decrease in life expectancy, many infections in these animals seem to be inapparent. Most healthy people have a relatively mild illness and fatal infections are rare; however, pregnant women may give birth to congenitally infected infants with severe defects of the brain and eye, and infections in organ transplant patients are life-threatening. Fatal illnesses have also been reported in some captive New World primates, particularly marmosets and tamarins.

Etiology

Lymphocytic choriomeningitis virus (LCMV) is a member of the genus *Mammarenavirus* and family *Arenaviridae*. There are many viral strains, which can differ in virulence. Some related arenaviruses (e.g., Dandenong virus) might cause similar diseases.

Species Affected

The house mouse (*Mus musculus*) is the primary reservoir host for LCMV. This virus can also be maintained by hamsters, and it or a variant occurs in the wood mouse (*Apodemus sylvaticus*) and the yellow-necked mouse (*A. flavicollis*). Some other rodents, such as guinea pigs, rats and chinchillas, can be infected but do not appear to be maintenance hosts.

LCMV can cause illness in New World primates of the family *Callitrichidae* (marmosets and tamarins), as well as Goeldi's monkeys (*Callimico goeldii*), which are close relatives in the family *Callimiconidae*. Some isolates also affect experimentally infected cynomolgus macaques (*Macaca fascicularis*) and rhesus macaques (*Macaca mulatta*), Old World primates of the family *Cercopithecidae*, though naturally acquired infections have not been reported in these species. Natural or experimental infections have been described in other mammals such as rabbits, dogs and pigs but, to date, no illnesses have been associated with these infections.

Zoonotic potential

Humans are susceptible to lymphocytic choriomeningitis.

Geographic Distribution

LCMV probably occurs worldwide wherever the house mouse can be found, i.e., on all continents except Antarctica. However, most clinical cases are described in North America and Europe, and the virus's distribution has not been clearly documented.

Transmission

Infected rodents can shed LCMV in saliva, nasal secretions, urine, feces, milk and semen. There seems to be minimal research on virus shedding in other animals, which are generally assumed to have little or no role in transmission; however, viral nucleic acids were found in the urine of affected primates, and one experimentally infected dog transmitted this virus to an uninoculated dog in close contact. LCMV can enter the body via aerosols or through broken skin and mucous membranes, including in bites or needlestick injuries. Monkeys can become infected after eating infected mice, and oral transmission in contaminated food or water is probably also possible in other species. Mechanical transmission by arthropods such as ticks, lice and mosquitoes has been demonstrated in the laboratory, but it is thought to play, at most, a minor role in nature. LCMV is known to cross the placenta in rodents and humans.

Mice and hamsters can become persistently infected with LCMV if they are exposed either *in utero* or soon after birth. Older animals usually clear the virus completely. Persistently infected mice can shed LCMV lifelong, while hamsters may excrete it for at least 8 months. These animals can also transmit the virus to their offspring *in utero*, perpetuating a cycle of inapparent infections in a rodent colony. All neonates do not necessarily become persistently infected; for instance, some hamsters infected at this time clear the virus around 3 months of age.

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People can become infected by contact with infected rodents or their secretions and excretions (e.g., urine, feces) in the environment. Contaminated cell cultures, which can be inapparently infected with LCMV, can be a source of laboratory-acquired infections. This virus can also be transmitted in organ transplants or vertically from mother to infant. The latter often occurs *in utero*, but infants can be infected after exposure to blood or vaginal secretions during birth. Except in these instances, people are not thought to transmit LCMV to others. However, investigators have noted that some sick transplant recipients had unusually high viral titers in their body fluids, raising the possibility of transmission to caregivers in close contact. Chronic infections have not been seen in humans, including congenitally infected infants.

Disinfection

LCMV is susceptible to most detergents and disinfectants including 1% sodium hypochlorite, lipid solvents and formaldehyde. Infectivity is lost quickly below pH 5.5 and above pH 8.5. It can also be inactivated by heat (55°C/ 131°F for 20 minutes), ultraviolet light or gamma irradiation.

Infections in Animals

Incubation Period

The incubation period is about 1-2 weeks in nonhuman primates and 5-8 days in some experimentally infected mice or guinea pigs. Persistently infected rodents are often asymptomatic for several months or more before ill effects become apparent.

Clinical Signs

Primates

LCMV causes callitrichid hepatitis in marmosets, tamarins and Goeldi's monkeys. This disease is characterized by multi-organ dysfunction involving the liver, spleen, pancreas, intestines, CNS and other organs. Some monkeys are found dead with no obvious premonitory signs. In other cases, animals may develop fever, anorexia, dyspnea, weakness and lethargy, followed by jaundice and, in some cases, petechial hemorrhages. Some animals may also have evidence of renal failure, seizures associated with meningoencephalitis, ataxia or other clinical signs. The disease often ends in prostration and death. Milder illnesses or asymptomatic infections also seem possible, as antibodies to LCMV have been found in some healthy animals during outbreaks.

Experimentally infected cynomolgus and rhesus macaques also developed multi-systemic disease. The clinical signs in these animals included severe dehydration, skin erythema, submucosal edema, necrotic foci in the buccal cavity, thrombocytopenia, signs of liver damage and

respiratory distress from pulmonary edema. Some infections were fatal, especially in animals given high doses of LCMV.

Mice, hamsters and other rodents

Many mice seem to be infected without obvious clinical signs, and most infected colonies are detected during routine monitoring or for other reasons, such as human illness or unexpected results from a research project. Persistently infected newborn mice can suffer growth retardation, especially during the first 3 weeks, but otherwise remain asymptomatic for a time. After 5-12 months, they may develop glomerulonephritis, with clinical signs of weight loss, ascites and nonspecific signs of illness (e.g., ruffled fur, hunched posture). Life expectancy can be decreased by a few months. Reproductive success may also be impaired, and infected female mice may give birth to stunted litters. Some mice infected after the neonatal period remain asymptomatic, but acute illnesses have also been described, with clinical signs that can include weakness, weight loss and other nonspecific signs (e.g., a rough hair coat), blepharitis, convulsions and tremors. Sick mice may either die within a few days to weeks or recover completely. LCMV can also cause generalized immunosuppression, and it has been associated with an increased incidence of lymphoma in some strains of mice.

Clinical signs reported in persistently infected hamsters are similar and can include runting, reduced litter sizes, glomerulonephritis and chronic generalized vasculitis. Sick hamsters may be anorectic and lethargic, with a rough coat, hunched posture and blepharitis. Weight loss may be noted and some affected animals die. Hamsters infected after the neonatal period may shed the virus for a time, but seem to remain asymptomatic.

Naturally acquired infections in rats and guinea pigs seem to be asymptomatic or mild in most cases. However, older descriptions suggest that some guinea pigs may develop pneumonia or, in rare instances, fatal paralysis due to meningoencephalitis. Experimentally infected guinea pigs became acutely ill, with fever and loss of condition, before recovering. Some of these animals had local erythema at the percutaneous inoculation site, teat rashes or erosions on the tongue. One study found that, when pregnant rats were infected with LCMV, some of their offspring were born with ocular disease and had elevated mortality during the first 2 months of life. Many of these animals had microscopic evidence of retinitis, and a few also had gross abnormalities such as retinal and vitreal hemorrhages, retinal detachment, vascular attenuation and corneal pannus.

Other animals

Infected dogs, rabbits and other mammals do not seem to have any clinical signs, but decreased growth was reported in experimentally infected neonatal rabbits.

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Post Mortem Lesions

Rodents

Common gross lesions in mice include hepatomegaly, splenomegaly, lymphadenopathy, and either swollen or shrunken and pitted kidneys from glomerulonephritis. Chronic glomerulonephritis is a common histopathological finding, together with vasculitis and lymphocytic infiltrates in other organs and tissues. Similar lesions have been seen in persistently infected hamsters.

Primates

Necropsy lesions in primates with callitrichid hepatitis may include jaundice, an enlarged and sometimes mottled liver (histopathology shows multifocal necrosis with acidophilic bodies and mild inflammatory infiltrates), splenomegaly, and subcutaneous and intramuscular hemorrhages. Some animals may have pleural and pericardial effusion, which is sometimes tinged with blood.

Diagnostic Tests

Rodents

LCMV, its antigens or nucleic acids can be detected in the tissues of infected rodents by virus isolation, immunostaining or reverse transcription polymerase chain reaction (RT-PCR), respectively. This virus can be isolated in a variety of cell lines including BHK21, L and Vero cells, and identified with immunofluorescence or other techniques. If necessary, it may also be recovered in LCMV-free mice.

Serology is useful for identifying infected rodent colonies, but it is not completely reliable in individual animals. Available serological tests may include the indirect immunofluorescence assay (IFA), virus neutralization (microplaque-reduction test) and ELISAs. Complement fixation tests have been used but are relatively insensitive.

Primates

Infectious virus, viral antigens or nucleic acids can be found in the serum, liver, spleen or other organs of callitrichids. Serology can also be used in diagnosis.

Treatment

Treatment of sick primates is supportive and symptomatic. There do not appear to be any studies of ribavirin, which may be considered in severely affected humans, in callitrichid hepatitis. Infected hamster and mouse colonies are often destroyed.

Control

Disease reporting

Veterinarians who encounter or suspect infection with LCMV should follow their national and/or local guidelines for disease reporting. State regulations should be consulted in the U.S.

Prevention

Wild rodents should be excluded from facilities that house laboratory rodents, pet rodents, breeding colonies and susceptible monkeys, and any infestations should be promptly controlled. Susceptible primates should not be fed mice that may be positive for LCMV, and biologics of mouse origin used in these animals must be LCMV-free. Captive mouse and hamster colonies should be obtained from LCMV-free populations and re-tested periodically to confirm that they remain virus-free. Good hygiene and disinfection can help prevent transmission between captive rodents, or from wild to captive rodents, on fomites. Filter cage covers can reduce aerosol transmission. Arthropods should be controlled.

It is difficult to be sure a new pet rodent is LCMV-free, as many infections are asymptomatic and serological testing is unreliable in individual rodents. In general, only active, alert animals with no obvious signs of disease (either in the animal or cage mates and nearby rodents) should be chosen. Pets should be selected, if possible, from a pet shop or other source that has a health monitoring program. Any cage or other equipment previously used for rodents should be cleaned and disinfected before use. Pet rodents that die should be handled with gloves and double-bagged, and their cage and environment should be cleaned and disinfected. If an animal dies soon after being taken home, the pet store should be informed.

Outbreaks in the pet rodent trade have been controlled by destroying the breeding stocks and disinfecting the premises, but some states allowed some animals (e.g., hamsters) received from an infected distributor to be sold or adopted with informed consent. Infected colonies of research animals are usually euthanized.

Morbidity and Mortality

LCMV can be a focal infection, with the virus established in one population of rodents without affecting others. Studies have found that its prevalence ranges from 0% to 60% in wild mice, with an average of about 9%. How often LCMV occurs in pet rodents is not known, but very few human cases have been associated with exposure to these animals. When infected pet hamsters have been found in the U.S., all of the animals were usually traced to a single breeding colony. Approximately 4% of the hamsters were infected at the distributor in one outbreak.

Morbidity and mortality are influenced by the species of animal and its age at infection, as well as the strain of the virus. Approximately half of all congenitally infected hamsters are thought to develop chronic disease, while the rest clear the virus around 3 months of age and remain healthy. Hamsters infected as adults do not usually become ill. Persistently infected mice remain asymptomatic for many months, but glomerulonephritis reduces overall life expectancy. How often mice become sick when they are exposed later in life is unclear; however, there are few

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reports of natural outbreaks, and subclinical infections might be the norm.

Callitrichid hepatitis in captive primates can occur either sporadically or as an outbreak. Twelve incidents with 67 deaths in marmosets, tamarins and/ or Goeldi's monkeys were reported in the U.S. between 1980 and 1995. Outbreak reports suggest that golden lion tamarins (*Leontopithecus rosalia*) might be especially susceptible.

Infections in Humans

Incubation Period

Nonspecific symptoms of acute disease generally appear 5-13 days after exposure and CNS signs in 2-3 weeks. Patients infected via solid organ transplants usually become ill within a few weeks of transplantation.

Clinical Signs

Most infections in healthy people are asymptomatic or characterized by a mild, self-limiting illness. The symptoms are flu-like and may include fever, fatigue, malaise, anorexia, headache, sore throat, myalgia (which can be severe), photophobia, and gastrointestinal signs such as nausea and vomiting. Coughing, a maculopapular rash, joint aches and chest pain are also possible. In most cases, the symptoms resolve without treatment within a few days.

Occasionally, a patient improves for a few days, then relapses with aseptic meningitis or, very rarely, meningoencephalitis. Uncommonly reported complications include myelitis, Guillain-Barre-type syndrome, cranial nerve palsies, transient or permanent hydrocephalus, orchitis, arthritis (especially in the joints of the hands) and parotitis. LCMV has also been implicated in pancreatitis, pneumonitis, myocarditis and pericarditis. The entire illness usually lasts 1 to 3 weeks, but a few patients with meningitis may have persistent symptoms (e.g., headaches, cognitive difficulties) for several months or more. Most people recover even from severe meningitis without sequelae. Permanent neurological damage is possible, particularly in cases of meningoencephalitis, but unusual. Deaths are rare.

In pregnant women, infections can result in abortion, acute neonatal meningitis or congenital CNS and/or ocular lesions in the fetus. The mother may or may not recall a febrile illness during the pregnancy. Common CNS defects include hydrocephalus, microcephaly, focal cerebral destruction, cerebellar hypoplasia and periventricular calcifications, but other signs (e.g., intracranial hemorrhage, sensorineural hearing loss) have also been reported. Ocular involvement usually appears as chorioretinitis, followed by chorioretinal scarring, and may lead to nystagmus or strabismus. Optic nerve atrophy, microphthalmia, vitritis, leukocoria and cataracts may also be seen. Systemic signs seem to be rare, but hepatosplenomegaly, thrombocytopenia, hyperbilirubinemia or non-immune hydrops fetalis (accumulation of fluid in at least 2 body sites) have been

documented in a few cases, and skin blisters were reported in one infant. The full spectrum of congenital disease may still be unknown.

Infants who survive may have severe neurological defects such as epilepsy, impaired coordination, visual loss/blindness, spastic diplegia or quadriplegia/quadruplegia, delayed development and mental retardation. Less severe cases with isolated cerebellar hypoplasia and symptoms of ataxia and mild to moderate learning disabilities have been reported occasionally. Some congenitally infected infants may eventually improve to some extent, but most neither improve nor become worse. Aspiration pneumonia can be a fatal complication.

Transplant patients usually become severely ill, and many cases have been fatal. The illness usually appears within weeks if the transplanted organ was the source of the virus, but cases can develop later if the virus is acquired from rodents. Common signs include fever, lethargy, anorexia and leukopenia, and in some cases, localized rash, abdominal pain, diarrhea or altered mental status. Respiratory compromise may be apparent, especially but not exclusively in lung transplant recipients. The illness quickly progresses to multisystem organ failure, hepatic insufficiency or severe hepatitis, coagulopathy, hypoxia and/or secondary bacteremia, and terminal shock. A similar illness was reported in three lymphoma patients who had failed conventional therapy and were given LCMV to induce tumor regression

Unusual syndromes have been described in rare instances. Fatal illnesses that resembled viral hemorrhagic fever were reported in a person who necropsied a monkey inoculated with brain tissue from a human encephalitis patient, and in another individual who autopsied the person who died. Viral hemorrhagic fever is a multi-systemic disease usually caused by arenaviruses other than LCMV, and characterized by vascular leakage, edema, bleeding tendencies, elevations in hepatic enzymes and, in some cases, neurological signs. (See the viral hemorrhagic fever factsheet for a full description of this disease.).

Diagnostic Tests

Serological tests, usually IFA or ELISA, are often used for diagnosis in humans. Antibodies may be found in blood or cerebrospinal fluid (CSF). Virus-specific IgM or a rising antibody titer can usually be detected in serum samples from acute cases; however, congenitally infected infants and their mothers generally have specific IgG from an infection earlier in the pregnancy, and IgM is absent. Virus-specific IgG has not been found in most transplant patients, even months after the infection, though some did have IgM.

RT-PCR is sometimes used to detect viral nucleic acids in the blood, CSF or other samples such as nasopharyngeal secretions, bronchoalveolar lavage fluid, amniotic fluid or biopsies of transplanted organs. Viral antigens are sometimes identified in transplanted organs by immunohistochemistry. Virus isolation is now infrequently

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attempted, but LCMV may be recovered from the blood or nasopharyngeal fluid early in the course of the disease, or from CSF in patients with meningitis. In congenitally infected infants, the virus has usually been cleared by birth.

Treatment

Treatment is symptomatic and supportive. Optimal management is not clear in transplant patients, but tapering of immunosuppression has been recommended, and ribavirin, sometimes combined with intravenous anti-LCMV immunoglobulin, has been tried in some patients. Whether these antiviral treatments provide significant benefit is currently unclear. Favipiravir, which was promising in mouse studies, is also being investigated.

Prevention

The risk of infection from wild mice can be decreased by ensuring that buildings and their surrounding areas are unattractive to rodents (e.g., by placing pet food and birdseed in rodent-proof containers); by sealing entry points for rodents with steel wool, caulking or metal; and by exterminating any rodents that enter the house. Live or dead mice should not be touched with the bare hands. Information on safely cleaning a rodent-infested area is available from sources such as the U.S. Centers for Disease Control and Prevention (CDC). It is particularly important to avoid aerosolizing the virus during this process.

Preventing infections in laboratory mice and susceptible primates, as described earlier (Infections in Animals), also decreases the risk of human illness. Personal protective equipment (PPE) and other precautions (e.g., to prevent bites) should be used when working with animals or conducting necropsies. Pregnant women and immunocompromised individuals should take special care to avoid contact with rodents, callitrichid primates, or closed spaces occupied by these animals, and should use appropriate PPE, including a respirator, if such contact is unavoidable. Cell lines should be bought from reputable companies that supply LCMV-screened cells.

Good hygiene, including hand washing, can reduce the risk of infections from pet rodents, their bedding and other fomites, especially those that may be contaminated with droppings or urine. Cages should be kept clean and free of soiled bedding. Cleaning is best done in a well-ventilated area or outside. Pet rodents should be kept away from the face. During pregnancy, they should be housed in a separate area of the home and cared for by another family member or friend. Another option would be to relocate the animal temporarily to someone else's home.

Organ donors are rejected if there is a suspicion they might be infected with LCMV, but screening for this virus is not routine. While LCMV is not generally considered a contagious disease in humans, high viral titers were found in the body fluids of some sick transplant patients, leading the investigators to suggest that universal precautions might be warranted for caregivers.

Morbidity and Mortality

Lymphocytic choriomeningitis is uncommonly reported in humans, but most infections are mild and are probably never identified. Laboratory personnel who handle rodents or infected cells have an increased risk of infection. A small number of studies in the U.S., South America and Europe also found antibodies to this virus in 1-10% of the general population, with two reports of higher prevalence (36% and 37%) in part of eastern Europe. Seroprevalence varies with the living conditions and exposure to mice, and may have been higher in the past.

Clinical cases tend to be sporadic, but outbreaks have occurred after exposure to infected laboratory rodents, tumor-cell lines used in research, or pet hamsters from infected colonies. In temperate climates, cases are more common in the fall or winter when wild mice move indoors. The incidence seems to be higher in adolescents and young adults. Most illnesses in healthy people seem to be mild, with a minority of patients developing aseptic meningitis (rarely encephalomyelitis), and an overall case fatality rate of < 1%. Complete recovery is the norm. In contrast, the disease has a very high morbidity and mortality rate in transplant patients, and nearly all of the patients died in early reports. Up to half survived in some recent incidents, where case clusters were generally recognized sooner.

Congenital lymphocytic choriomeningitis seems to be uncommon: as of 2018, there were approximately 75 published reports of this disease. The probability that a woman will become infected after being exposed to rodents, the frequency with which LCMV crosses the placenta, and the likelihood of clinical signs in the infant are still poorly understood. The prognosis for severely affected infants appears to be poor. In one case series, 35% of congenitally infected infants had died by the age of 21 months. Most of the rest had serious, permanent neurological defects, though there were also less severe cases and a few children were normal. It should be noted that less severely affected or asymptomatic infants may not be recognized, as LCMV testing is not routine.

Internet Resources

Centers for Disease Control and Prevention (CDC).
Lymphocytic choriomeningitis
<https://www.cdc.gov/vhf/lcm/index.html>

Public Health Agency of Canada.
Pathogen Safety Data Sheets
<https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment.html>

The Merck Manual
<https://www.merckmanuals.com/professional>

The Merck Veterinary Manual
<https://www.merckvetmanual.com/>

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