Importance

Lymphocytic choriomeningitis virus (LCMV) is a pathogen, normally carried in rodents, which can cause aseptic meningitis and other conditions in humans. Most people experience 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. In a few instances, this virus has been transmitted in transplanted organs, usually resulting in fatal disease. LCMV infections in rodents are often subclinical, although acute clinical signs or chronic effects may be seen in some animals. Some strains of this virus can cause life-threatening illness in New World monkeys. LCMV is also a potential bioterrorist weapon.

Etiology

The lymphocytic choriomeningitis virus is a member of the genus Arenavirus and family Arenaviridae. There are many strains of this virus with varying pathogenicity.

LCMV is classified in the Lassa-Lymphocytic choriomeningitis (Old World) serocomplex of arenaviruses. Two recently discovered viruses in this complex might be able to cause similar illnesses. Kodoko virus, which was detected in Mus Nannomys minutoides (pygmy mice) in Guinea, West Africa, is closely related to LCMV. Its potential to cause disease in humans is unknown. Dandenong virus was isolated from Australian transplant patients who developed a fatal, febrile illness with encephalitis. The virus was transmitted in organs from a donor who had recently returned from a trip to the former Yugoslavia. Its reservoir host, which is probably a rodent, is unknown.

Geographic Distribution

LCMV probably occurs worldwide wherever its natural host, the house mouse (Mus musculus) can be found. This rodent has become established on all continents except Antarctica. Although serological evidence suggests that LCMV circulates in Africa, cross-reactions can occur with other arenaviruses and there is no definitive evidence of its presence there.

Transmission

Infected rodents can shed LCMV in the saliva, nasal secretions, urine, milk, feces and semen. This virus can be transmitted in aerosols, or through abraded skin and mucous membranes. It can be acquired via bites. Monkeys have become infected after eating infected mice; oral transmission in contaminated food or water may also be possible in other species. Transplacental transmission can occur in rodents and humans.

Viral persistence and shedding varies with the host and its age when it is infected. Persistent infections occur in some mice (M musculus) and hamsters that are exposed in utero or as newborns. These animals can shed the virus lifelong. Other mice and hamsters infected during the neonatal period may develop only transient viremia. Rodents infected after this time usually clear the virus completely. Chronic infections have not been reported in other species, including congenitally infected humans.

People can become infected by direct contact with infected rodents, or indirect contact with the virus in excretions and secretions from rodents (e.g., by inhalation). Human infections have been documented after contact with infected mice, hamsters and guinea pigs. Zoonotic transmission from other wild and pet rodents may be possible, and seroconversion has been reported after bites from infected primates. LCMV, which is a noncytopathic virus, can also contaminate some cell cultures and cause laboratory-acquired infections. Person-to-person transmission does not seem to occur, except in organ transplants or from mother to child across the placenta.

LCMV has been isolated from fleas, ticks, cockroaches and Culicoides and Aedes mosquitoes. Ticks, lice and mosquitoes have been shown to transmit this virus mechanically in the laboratory. If arthropod-mediated spread occurs in nature, it is thought to play only a minor role in the epidemiology of this disease.
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Disinfection

LCMV is susceptible to most detergents and disinfectants including 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde and formaldehyde. Infectivity is lost quickly below pH 5.5 and above pH 8.5. LCMV can also be inactivated by heat, ultraviolet light or gamma irradiation.

Infections in Humans

Incubation Period

In humans, the symptoms of acute disease usually appear 5 to 13 days after exposure. In cases with meningitis, central nervous system (CNS) signs usually develop 15 to 21 days after infection. Patients infected in solid organ transplants have become symptomatic within a few weeks of transplantation.

Clinical Signs

Most infections in immunocompetent individuals 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, photophobia, and gastrointestinal signs such as nausea and vomiting. Coughing, rushes, joint aches and chest pain are sometimes seen. 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.

Patients with meningitis may have a stiff neck, fever, headache, myalgia, nausea and malaise. Occasionally, meningitis occurs without a prodromal syndrome. Meningoencephalitis is characterized by more profound neurological signs such as confusion, drowsiness, sensory abnormalities and motor signs. Uncommonly reported complications include myelitis, Guillain-Barre-type syndrome, cranial nerve palsies, transient or permanent hydrocephalus, sensorineural hearing loss, orchitis, arthritis and parotitis. LCMV infections have also been implicated in pancreatitis, pneumonitis, myocarditis and pericarditis. The entire illness usually lasts 1 to 3 weeks, and most people recover even from severe meningitis without sequelae. However, temporary or permanent neurological damage is possible in all CNS infections, particularly in cases of meningoencephalitis. Deaths are rare. Chronic infections have not been reported in humans.

Prenatal infections can result in abortions, acute neonatal meningitis or severe developmental defects in the fetus. The mother may or may not recall a febrile illness during the pregnancy. Common CNS defects in the fetus include hydrocephalus, microcephaly, cerebellar hypoplasia and periventricular calcification. Chorioretinitis, which is followed by chorioretinal scarring, is the most common ocular lesion. Other ocular defects including optic atrophy, microphthalmia, vitreitis, leukokoria and cataracts can also be seen. Most of the infants in one case series were of normal birth weight, although 30% were underweight. Some congenitally infected infants may eventually improve to some extent, but most neither improve nor become worse. Aspiration pneumonia can be a fatal complication. Infants who survive may have severe neurological defects including epilepsy, impaired coordination, visual loss or blindness, spastic diplegia or quadriplegia, delayed development and mental retardation. Less severe cases with isolated cerebellar hypoplasia and symptoms of ataxia and jitteriness have been reported occasionally. There have also been rare cases with evidence of chorioretinitis but without neurological signs. Systemic signs seem to be rare, but hepatosplenomegaly, thrombocytopenia and hyperbilirubinemia 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.

Patients infected in solid organ transplants have developed a severe fatal illness, starting within weeks of the transplant. In the cases reported to date, the initial symptoms included fever, lethargy, anorexia and leukopenia, and quickly progressed to multisystem organ failure, hepatic insufficiency or severe hepatitis, dysfunction of the transplanted organ, coagulopathy, hypoxia, multiple bacteremias and shock. Localized rash and diarrhea were also seen in some patients. Nearly all cases have been fatal.

Other rare syndromes have also been described. Fatal illnesses that resembled viral hemorrhagic fever were reported in one person who had conducted a necropsy on an infected monkey, and in an individual who autopsied the person who died. The monkey had been inoculated with brain tissue from a patient with encephalitis. Severe cases of viral hemorrhagic fever, a disease that is usually caused by arenaviruses other than LCMV, are characterized by a multisystemic disease with hypotension, edema, shock, bleeding tendencies and neurological signs. (See the viral hemorrhagic fever factsheet for a full description of this disease.) Fatal multisystemic illness was also reported in three lymphoma patients who had failed conventional therapy and had been given LCMV to induce tumor regression.

Communicability

LCMV does not seem to be transmitted from person to person, except to the fetus in utero or in transplanted organs.

Diagnostic Tests

Lymphocytic choriomeningitis is usually diagnosed in humans by serology, but virus isolation and other tests can also be used.

Acute infections can be diagnosed by detecting virus-specific IgM or a rising antibody titer. Antibodies to LCMV may also be found in the cerebrospinal fluid (CSF).
congenital infections, the virus has usually been cleared by the time the infant is born; in most cases, both the mother and infant have specific IgG, and IgM is absent. The most commonly used serological tests are the indirect immunofluorescence assay (IFA) and enzyme-linked immunosorbertent assays (ELISAs). Both tests can detect either IgM or IgG. The ELISA test for LCMV antibodies may not be widely available; in the U.S., it is performed at the Special Pathogens Branch at the Centers for Disease Control and Prevention (CDC). The complement fixation test is relatively insensitive.

Reverse transcription polymerase chain reaction (RT-PCR) tests may detect nucleic acids in the blood and CSF.

Virus isolation is not used for diagnosis in most cases. In the U.S., this test is also available at the CDC. LCMV may be isolated 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. LCMV can be grown in a variety of cell lines including BHK21, L and Vero cells, and it may be identified with immunofluorescence. A diagnosis can also be made by the intracerebral inoculation of blood or CSF into mice.

LCMV cannot always be detected in donors who have transmitted this virus to transplant recipients. Three clusters of transplant-associated cases were reported in the U.S. from 2005 to 2010. Neither of the first two donors had a history of an acute infectious disease, and RT-PCR tests and serology did not detect LCMV. In one case, a genetically identical virus was, however, detected in the donor’s pet hamster. The third donor died of an illness characterized by fever and neurological signs, and an antemortem serum sample later tested positive for LCMV-specific IgM and IgG.

**Treatment**

Treatment is symptomatic and supportive. Children with hydrocephalus often need a ventriculoperitoneal shunt. Ribavirin is not used routinely in the treatment of lymphocytic choriomeningitis; however, it has been promising in anecdotal reports, and has been recommended especially for immunocompromised patients and others who are severely ill. The only survivor of a transplant-associated LCMV infection was treated with ribavirin and simultaneous tapering of the immunosuppressive medications. Ribavirin has not been evaluated yet in controlled clinical trials. It is also teratogenic.

**Prevention**

Most human infections result from exposure to infected mice. The risk of infection from wild mice can be decreased by ensuring that buildings and their surrounding areas are unattractive to rodents, and by preventing these animals from entering the home. For example, food that may attract rodents (including pet food and birdseed) should be kept in rodent-proof containers, and holes where mice may enter the house should be sealed with steel wool, caulk or metal. Wild mice should be exterminated or removed if they are present in the home. Direct contact should be avoided; live or dead mice should not be touched with the bare hands. Information on safely cleaning a rodent-infested area is available from the CDC. It is particular important to avoid aerosolizing the virus during this process.

Laboratory colonies of domesticated mice should be tested regularly for LCMV. The risks associated with handling wild-caught rodents should be kept in mind by those who work with them. Personal protective equipment (PPE) and other precautions should be used as appropriate. Safe handling practices to prevent bites, with appropriate PPE, should also be used when handling or performing necropsies on New World primates. Seroconversion occurred in two zoo veterinarians who were bitten by infected primates or performed necropsies during outbreaks of callitrichid hepatitis. Cell lines susceptible to LCMV should be bought from reputable commercial suppliers that supply screened cells.

Cases of lymphocytic choriomeningitis are rarely attributed to pet rodents. Good hygiene can help prevent infections from these animals. The hands should be washed with soap and water after handling rodents, their cages, bedding and any other object 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. Young children should be supervised when handling rodents, to ensure that they practice good hygiene. Because tests are for LCMV are unreliable in individual animals, the CDC does not recommend testing pet rodents for this virus.

Particular care should be taken to avoid contact with rodents during pregnancy. Pregnant women should avoid touching wild or pet rodents or their droppings, and they should not stay for long periods in rooms where these animals are present. For the duration of the pregnancy, pet rodents should be kept in a separate area of the home and cared for by another family member or friend. Another option would be to care for the animal temporarily in someone else’s home. Infestations by wild mice should be handled by a professional pest control company or another member of the household. Pregnant women who work with rodents should wear gloves, gowns, and face masks. Precautions to avoid infections from callitrichid primates are also advisable during pregnancy.

**Morbidity and Mortality**

Lymphocytic choriomeningitis is uncommonly reported in humans; however, most infections are mild and are probably never diagnosed. Serological surveys suggest that approximately 1-5% of the population in the U.S. and Europe has antibodies to LCMV. The prevalence varies with the living conditions and exposure to mice, and may
Lymphocytic Choriomeningitis

Incubation Period

After experimental inoculation, the incubation period in adult mice is 5 to 6 days. Congenitally or neonatally infected mice and hamsters do not become symptomatic for several months or longer.

Clinical Signs

Mice

In mice, the clinical signs vary with the host’s resistance and age at infection, as well as the strain of the virus. Mice infected in utero or during the first few days after birth may become persistently infected and shed the virus for life. These mice can suffer growth retardation, particularly during the first three weeks, but otherwise remain asymptomatic for several months. After 5 to 12 months, persistently infected mice may develop glomerulonephritis accompanied by weight loss, emaciation, ruffled fur, hunched posture and ascites. Life expectancy can be decreased by a few months. In addition, reproductive success may be impaired, and infected female mice may give birth to stunted litters.

In mice more than a few days old, LCMV is recognized as foreign. Some infected mice remain asymptomatic and clear the virus. Others become acutely ill; the clinical signs may include blepharitis, weakness, convulsions, tremors, photophobia, growth retardation and a rough hair coat. Mice with acute disease either die within a few days to weeks or recover completely. These mice do not become chronically infected. In some strains of mice, LCMV infection is associated with an increased incidence of lymphoma. Generalized immunosuppression can also occur.

Choriomeningoencephalitis is usually seen only after experimental intracerebral inoculation.

Hamsters

Runting, reduced litter sizes, glomerulonephritis and chronic generalized vasculitis have been reported in some persistently infected hamsters. Lethargy, anorexia and a rough coat may be seen in the early stages. Later, there may be weight loss, a hunched posture and blepharitis. Affected mice may die. Hamsters infected after the neonatal period become viremic and may shed the virus for a time, but seem to remain asymptomatic.

Rats

Experimental intracerebral infection of suckling rats results in microcephaly, retinitis and the destruction of several brain regions, leading to permanent abnormalities of movement, coordination, vision and behavior.
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**Primates**

LCMV causes callitrichid hepatitis in New World primates. The initial signs are nonspecific and may include fever, anorexia, dyspnea, weakness and lethargy. Jaundice is characteristic and petechial hemorrhages may develop. These signs are often followed by prostration and death.

**Communicability**

In rodents, LCMV is shed in urine, saliva, feces, milk and semen. Mice infected *in utero* or during the neonatal period may shed the virus for life. Some persistently infected hamsters also shed the virus for at least eight months, while others seem to clear the virus at approximately three months of age. Hamsters infected after the neonatal period can shed the virus for 3 to 6 months. Vertical transmission has been reported in mice and hamsters.

**Post Mortem Lesions**

**Rodents**

Gross lesions reported in mice include hepatomegaly, splenomegaly, lymphadenopathy, and swollen or shrunken and pitted kidneys due to glomerulonephritis. Histological findings in persistently infected mice often include chronic glomerulonephritis. In these mice, there may also be vasculitis and lymphohytic infiltrates in many organs and tissues including the liver, spleen, lung, kidneys, pancreas, blood vessels, meninges and brain.

Chronic glomerulonephritis and chronic generalized vasculitis have been reported in persistently infected hamsters.

**Primates**

Necropsy lesions in primates with callitrichid hepatitis may include jaundice, hepatomegaly, splenomegaly, and subcutaneous and intramuscular hemorrhages. Pleural and pericardial effusion, sometimes sanguineous, may be seen. On histology, multifocal necrosis with acidophilic bodies and mild inflammatory infiltrates are typically found in the liver. Other organs including the spleen, lymph nodes, adrenal glands, intestine, pancreas and central nervous system may also be affected.

**Diagnostic Tests**

**Rodents**

In rodents, lymphocytic choriomeningitis can be diagnosed by virus isolation, the detection of viral antigens or serology.

LCMV can be isolated in a variety of cell lines including BHK21, L and Vero cells; the virus may be identified with immunofluorescence. Animal inoculation into mice can also be used to recover this virus. Immunostaining can detect viral antigens in tissues including the liver, and RT-PCR can detect viral RNA.

Serological tests that have been used in rodents include immunofluorescence (IFA), the microplaque-reduction test for neutralizing antibody, and ELISAs. Complement fixation has been employed, but it is relatively insensitive. Serology is useful in rodent colonies, but it is not completely reliable for identifying infections in individual rodents.

**Primates**

In monkeys, viral antigens or nucleic acids can be detected by immunostaining or *in situ* hybridization of the liver. Virus isolation, RT-PCR and serologic tests can also be used.

**Treatment**

There is no specific treatment for lymphocytic choriomeningitis. Infected hamster and mouse colonies are usually destroyed. Treatment in non-human primates is supportive and symptomatic.

**Prevention**

Wild rodents should not be allowed to contact pet rodents, breeding colonies, laboratory rodents or New World monkeys. Precautions such as keeping feed in sealed containers can make facilities less attractive to these animals. Mice and rats that enter buildings should be exterminated. Primates should not be fed mice that may be positive for LCMV. Captive mouse and hamster colonies should be obtained from LCMV-free populations. These animals should be re-tested periodically to confirm that they remain free of this virus. Good hygiene and disinfection can help prevent transmission between captive rodents, as well as from wild to captive rodents, on fomites. Filter cage covers can reduce aerosol transmission. Arthropods should also be controlled.

When bringing a new pet rodent into the home, it is difficult to be sure it is LCMV-free, as many infections are asymptomatic. In general, only active, alert animals with no obvious signs of disease (either in the individual animal or in 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 reuse. Serological testing is not reliable for ensuring that an individual rodent is LCMV-free; testing of pets is not recommended by the CDC. 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, as the animal might have died of an infectious disease that has affected other animals in the shop.

Infected colonies of research animals are usually euthanized. Outbreaks in pet rodents have been controlled by destroying the breeding stocks and disinfecting the premises. If there are biosecurity issues that allow transmission from wild mice, they must also be corrected. Some individual states have allowed some animals (e.g., hamsters) received from an infected distributor to be sold or
adopted with an information leaflet or informed consent; in other cases, the sale of all animals that might have been exposed was prohibited. LCMV infections are reportable by veterinarians in some states.

**Morbidity and Mortality**

LCMV infections are focal; this virus is often carried in one population of rodents without affecting others. Estimates of its prevalence in wild mouse populations range from 0% to 60%, with an average prevalence of 9%. The incidence of LCMV in pet rodents is unknown; however, very few human cases have been associated with exposure to pets. In the U.S., when infected pet hamsters have been found, all of the animals have usually been traced to a single breeding colony. In the transplant-associated cases linked to a pet hamster in 2005, two other hamsters and a guinea pig at the pet shop, and approximately 4% of the hamsters at the distributor, were also infected.

Morbidity and mortality rates vary with the species of animal and its age at infection, as well as the strain of the virus and route of exposure. Neonatally and congenitally infected mice remain asymptomatic for many months, but the onset of glomerulonephritis reduces overall life expectancy. The morbidity rate in naturally infected post-neonatal mice is unknown; however, subclinical disease may be the most common form, as few natural outbreaks have been reported.

In hamsters, approximately half of all congenitally infected animals clear the virus when they are approximately three months old and remain healthy; the remaining animals develop chronic disease. Hamsters infected as adults usually remain asymptomatic.

Callitrichid hepatitis is reported to be highly fatal in naturally infected marmosets and tamarins in zoos. Since 1980, 12 outbreaks with 57 deaths have been reported in the U.S. In experimentally infected rhesus macaques, three of four animals became fatally ill when inoculation was by the intravenous route. In contrast, inoculation by the intragastric route usually led to asymptomatic infections, with occasional disease and few deaths.

**Internet Resources**

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/nctidod/dvrd/sph/mnpages/dispages/lcmv.htm

Medical Microbiology
http://www.ncbi.nlm.nih.gov/books/NBK7627/

Public Health Agency of Canada.
Material Safety Data Sheets

The Merck Manual
http://www.merck.com/pubs/mmanual/
Lymphocytic Choriomeningitis


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