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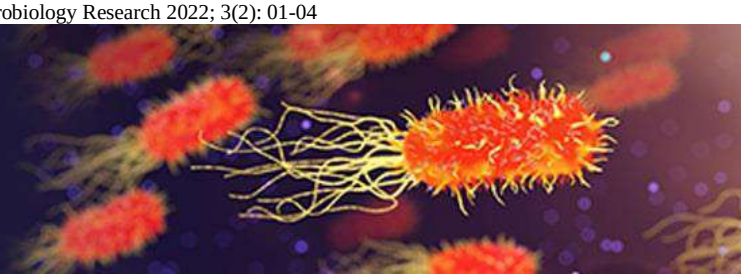

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Lymphocytic choriomeningitis: An emerging and re-emerging rodent-borne viral zoonotic disease

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Abstract
Lymphocytic choriomeningitis is an infectious emerging and re-emerging of zoonosis of public health significance that is caused by lymphocytic choriomeningitis virus that belongs to the *Arenaviridae* family and is an important cause of neurological disease in humans. The common house mouse, *Mus musculus*, is the natural host for lymphocytic choriomeningitis virus. The infected rats and mice shed huge amounts of the virus in their saliva, urine, feces, and nasal secretions. When feces, saliva, or urine from lymphocytic choriomeningitis virus infected rodents is inhaled or swallowed, acquired primary infection ensues. Lymphocytic choriomeningitis virus can infect the fetus after crossing the placenta. Lymphocytic choriomeningitis virus infection in humans is usually asymptomatic, although it can cause aseptic meningitis or, in rare cases, meningoencephalitis. The infection due to lymphocytic choriomeningitis virus can be severe and most often fatal among transplant patients. IgM and IgG antibodies in the cerebrospinal fluid and serum are frequently used to make a laboratory diagnosis. Virus can be found in the cerebrospinal fluid during the acute stage of disease using PCR or virus isolation technique. Because there is no cure for the disease, treatment is symptomatic and supportive. Limiting the entry of wild mice into facilities, wearing protective clothes, and taking caution while handling affected animals or tissues, as well as basic hygiene measures, can all help to prevent this rodent borne viral disease?

Keywords: Lymphocytic choriomeningitis, lymphocytic choriomeningitis virus, *Mus musculus*, public health, rodent, zoonosis

Introduction
Lymphocytic choriomeningitis is a zoonotic disease caused by lymphocytic choriomeningitis virus that belongs to the genus *Arenavirus* (Pal, 2007) [19]. Although rodents can become ill or experience other negative consequences, such as a reduction in lifespan, many infections in these animals appear to be undetectable. Some captive New World monkeys, particularly marmosets and tamarins, have died from diseases. The infections in healthy persons are usually mild, and fatal infections are uncommon; nevertheless, pregnant women may give birth to congenitally infected infants with serious brain and eye impairments, and infections in organ transplant recipients can be deadly (Acha and Szyfres, 2003; Rovid, 2020) [1, 23].
Lymphocytic choriomeningitis virus infection is normally asymptomatic or moderate and self-limiting, but serious infection, such as meningitis and encephalitis can occur in rare cases (Barton, 1996) [4]. Such an infection can be fatal in organ transplant recipients and immunocompromised patients (Palacios *et al.*, 2008) [20]. The congenital infections can cause mental impairment and eyesight problems for the rest of life (Barton *et al.*, 1993) [5]. This review is intended to fill the gap on the current state of knowledge on lymphocytic choriomeningitis and counter measures on the prevention of this viral zoonotic disease.

Etiology
Lymphocytic choriomeningitis is a viral infection spread by rodents caused by lymphocytic choriomeningitis virus (LCMV), which was first discovered in 1933 (CDC, 2014) [8]. Lymphocytic choriomeningitis virus is a member of the *Arenavirus* genus, which belongs to the *Arenaviridae* family (Bonthius, 2012) [7]. Lymphocytic choriomeningitis virus is a bi-segmented, negative sense RNA virus that causes lymphocytic choriomeningitis (Bishop and Auperin, 1987) [6]. L (7.5kb) and S (3.5kb) are the names of the two gene segments. The viral polymerase and tiny zinc-binding protein are encoded by the L segment, while the glycoprotein precursor and nucleoprotein are encoded by the S segment (Montali, 1993) [18].

Different LCMV isolates have found to exhibit high genetic heterogeneity and phenotypes of clinical course throughout time. However, a variety of LCMV strains can cause serious disease in humans (Amman *et al.,* 2007; Emonet *et al.,* 2007) [2, 11]. Lymphocytic choriomeningitis virus is susceptible to most detergents and disinfectants including 1% sodium hypochlorite, lipid solvents and formaldehyde. Below pH 5.5 and above pH 8.5, infectivity is rapidly lost. Heat (55ºC/131ºF for 20 minutes), ultraviolet light, or gamma irradiation can also inactivate it (Pfau, 2006) [22].

Epidemiology

Armstrong and Lillie discovered lymphocytic choriomeningitis virus (LCMV) from the cerebrospinal fluid of a patient with meningoencephalitis during the St. Louis encephalitis outbreak (St. Louis, Missouri, USA) in 1933 (Traub, 1935) [25]. The principal reservoir host for LCMV is the house mouse (*Mus musculus*). This virus can be maintained by hamsters, and it or a variant of it can be found in the wood mouse (*Apodemus sylvaticus*) and the yellow-necked mouse (*Apodemus flavicollis*). Guinea pigs, rats, and chinchillas are examples of rodents that can be infected but do not appear to be maintenance hosts (Rovid, 2020) [23]. Humans have been warned about the dangers of being in close proximity to natural populations of these rodents (James *et al.,* 2019) [15].

Lymphocytic choriomeningitis virus is likely to be found on every continent except Antarctica. The virus's distribution has not been well established, and the majority of clinical cases have been reported in North America and Europe (CDC, 2021) [9]. Human cases of lymphocytic choriomeningitis are uncommon; however, the majority of infections is mild and goes unnoticed. Laboratory workers who work with rodents or infected cells are more likely to become infected. Antibodies to this virus were discovered in 1-10% of the general population in a small number of investigations in the United States, South America, and Europe, with two reports of higher frequency (36% and 37%) in parts of Eastern Europe. The seroprevalence varies depending on living conditions and mouse exposure, and it was maybe higher in the past (Rovid, 2020) [23].

Transmission

The common host of LCMV is house mice (*Mus musculus*) (CDC, 2014) [8]. Infected mice bites, inhalation of aerosolized droplets of contaminated body fluids, or inoculation of contaminated materials into broken skin, the eyes, or the mouth are all modes of transmission to humans (Emonet *et al.,* 2007; Pal, 2007) [11, 19]. Person-to-person transmission has not been documented, with the exception of vertical transmission from an infected mother to her fetus and, in rare cases, organ donation (CDC, 2014) [8]. In the laboratory, mechanical transmission by arthropods like ticks, lice, and mosquitoes has been established, but it is assumed to play only a minimal role in nature (Rovid, 2020) [23].Occasionally, the infection can also occur by the bite of mice (Pal, 2007) [19].

Clinical Signs

In Humans

Lymphocytic choriomeningitis has a 1 to 2 week incubation period (Pal, 2007) [19]. In healthy persons, most infections are asymptomatic or cause a mild, self-limiting infection (Yuill, 2021) [26]. The virus produces biphasic febrile illness, which starts with any or all of the following symptoms: fever, malaise, lack of appetite, muscle aches, headache, nausea, and vomiting in the initial phase. Sore throat, cough, joint discomfort, chest pain, testicular pain, and parotid (salivary gland) pain are some of the less common symptoms. A second wave of illness may arise after a few days of recuperation. Meningitis (fever, headache, stiff neck, etc), encephalitis (drowsiness, disorientation, sensory problems, and/or motor abnormalities, such as paralysis), or meningoencephalitis (brain and meninges inflammation) are some of the symptoms (CDC, 2014) [8]. Immunocompromised people (such as solid organ transplant recipients) might develop a multisystem organ involvement syndrome, which can include encephalitis/seizures, respiratory failure, leukopenia, thrombocytopenia, coagulopathy, renal/liver dysfunction, and hemorrhagic foci in various tissues (Fischer *et al.,* 2006; Peter, 2006) [12, 21]. It is mentioned that the infection during pregnancy might lead to miscarriage or birth defects (Barton *et al.,* 1995) [3].

In Animals

In nonhuman primates, the incubation period is about 1-2 weeks. Multi-organ dysfunction including the liver, spleen, pancreas, intestines, CNS, and other organs is seen in primates with this condition. Some monkeys are discovered deceased with no visible evidence of illness. Animals may experience fever, anorexia, dyspnea, weakness, and lethargy in other circumstances. Renal failure, seizures linked with meningoencephalitis, ataxia, and other clinical symptoms may also be present in some animals. Prostration and death are common outcomes of the condition. Milder diseases or infections with no symptoms appear to be a possibility. Infected dogs, rabbits, and other mammals do not appear to show any clinical indications, but experimentally infected neonatal rabbits showed impaired (Hotchin, 1971; Rovid, 2020) [14, 23].

Diagnosis

Patients with rat exposure with an acute illness, such as aseptic meningitis or encephalitis, are suspected of having lymphocytic choriomeningitis (Yuill, 2021) [26]. Low white blood cell count (leukopenia) and low platelet count (thrombocytopenia) are the most common laboratory abnormalities in the early stages of the disease (CDC, 2014) [8]. Assessment of acute and convalescent immunoglobulin M (IgM) and immunoglobulin G (IgG) titers in serum and cerebrospinal fluid is the preferred diagnostic method (CSF). The sensitivity of an enzyme-linked immunosorbent test (ELISA) is higher than that of an immunofluorescence assay (IFA). Complement fixation is insensitive and should not be employed (Lapoová *et al.,* 2016) [27]. Immunohistochemistry, virus culture, and reverse transcription-polymerase chain reaction (RT-PCR) may also be helpful (Seregin *et al.,* 2015) [24].

Treatment

Treatment is symptomatic and supportive in humans (Rovid, 2020) [23]. Patients should be admitted to the hospital if they develop aseptic meningitis, encephalitis, or meningoencephalitis, and ribavirin treatment should be explored (Yuill, 2021) [26]. Ribavirin has anti-LCMV action *in vitro* and has been administered successfully in transplant recipients with severe infections (Fischer *et al.,* 2006) [12]. *In vitro*, favipiravir has been demonstrated to suppress LCMV.

In animal models, it has also shown promise in lowering the mortality of other arenavirus infections. More research is needed to see if favipiravir can be used safely to treat infections with arena viruses, such as LCMV, in humans (Furuta *et al.*, 2017) [13]. In some cases, anti-inflammatory medicines (e.g., corticosteroids) may be considered (Yuill, 2021) [26].

Prevention and Control

For post-exposure prophylaxis, there are no evidence-based standard drugs available: As a result, preventing stab wounds with contaminated sharp objects, infected mouse bites, and inhalation of contagious droplets is critical in protecting laboratory workers from serious infection, which can lead to epidemics (Knust *et al.*, 2014) [16]. Laboratory employees must be educated on the potential transmission channels and clinical manifestations of LCMV, as well as receive repeated instructions on how to safely handle the virus. Working with LCMV necessitates the use of high-quality gloves, goggles, and protective gowns, as well as the installation of proper ventilation systems when animals are handled. Surfaces should be disinfected on a regular basis with certified anti-LCMV products. In addition, a standard operating protocol for the handling of inadvertent virus exposure should be available. Pregnant women and immunocompromised people should be warned that even a tiny amount of this pathogenic virus can cause a serious, life-threatening infection (Drager *et al.*, 2019) [10]. Infections from pet rodents, their bedding, and other fomites, especially those infected with droppings or urine can be reduced with good hygiene, including hand washing. Cages should be kept clean and filthy bedding should be removed. Cleaning is best done outside or in a well-ventilated location. Pet rodents should not be let near the face. They should be kept in a different section of the house throughout pregnancy and cared for by another family member or friend. Another alternative is to temporarily relocate the animal to someone else's home (Rovid, 2020) [23]. It is important to mention that dead rodents should be incinerated to prevent the spread of infection (Pal, 2007) [19].

Conclusion

Lymphocytic choriomeningitis is viral infection of the membranes protecting the brain and spinal cord, as well as the cerebrospinal fluid. The common house mouse, *Mus musculus*, is a natural carrier of the virus. Despite the fact that virus has the capacity to spread globally; human cases have only been identified and documented in Europe and the Americas. The most common way for humans to become infected is through contact with infected animals' fluids or excretions. The prevalence of lymphocytic choriomeningitis virus infection in transplant donors is a growing problem. The infection can cause a variety of clinical signs, and it can even be asymptomatic in immunocompetent people. A typical LCM has two phases: a period of fever and vermeil, followed by a CNS phase in which the virus no longer circulates, antibodies are identified in the serum, but the virus remains in the CN. For many years, indirect immunofluorescence was used to diagnose lymphocytic choriomeningitis. Virus isolation can also be used to validate the presence of virus in animal colonies with correct sampling. The simplest way to avoid lymphocytic choriomeningitis is to take hygienic measures while dealing with wild and pet mice.

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Contribution of authors

During the writing of the manuscript, all of the authors contributed equally. They read the final manuscript and gave it their approval for publishing.

Conflict of interest

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