GV-SOLAS
Gesellschaft für Versuchstierkunde
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Expert Information

From the Working Group on Hygiene

Implication of infectious agents on results of animal experiments

Lymphocytic Choriomeningitis Virus

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Contents

Lymphocytic Choriomeningitis Virus (LCMV)

Background

- LCMV is the causal agent of lymphocytic choriomeningitis in humans.[1,2,3,4]
- LCMV was first isolated as cause of aseptic meningitis among hospitalized patients in St. Louis in the early 1930s.[5,6]
- After 1935 many lab colonies of mice were found to be infected with LCMV in the USA[7] and Japan.[8]
- Wild house mouse was identified as reservoir of LCMV in the late 1930s.[9]
- Between 1933 and 2008 over twenty-three different virus strains with high genetic diversity were identified.[10]

Prevalence

- Prevalence of LCMV among wild mouse populations: In Germany (in the early 1960s) 3% of samples were positive[11], in the UK about 4%[12], in Japan 9-25%[13,14], in Australia 0%[15], in the USA 3.9-13.4%[16], in China 2 %[17], and in Spain up to 9 %[18]
- The prevalence of LCMV among laboratory mice is actually low: North America 1%, Europe 2%[19] respectively 0%[20,21], France 2%[22], Taiwan 4%[23], Japan 2-5.6%.[24]
- Prevalence of LCMV in hamster inbred strains[25,26] is up to 2.2 % of hamsters.[24]
- Transplantable hamster tumors, different cell lines and monoclonal antibodies are potential carriers of LCMV.[27,28]
- In laboratory rats, LCMV is normally not found.[19,20,21,23]
- Prevalence of LCMV antibodies in human populations range from 2% to 5% indicating previous exposure and infection.[16,18,29,30]

Host species

- Natural hosts for LCMV are laboratory and wild mice, pet and laboratory hamsters. These hosts transmit virus.[31,32,33]
- Aberrant hosts are most rodents, dogs, non-human primates and humans.[12,16,34-36] These hosts do not transmit virus.[37,38]
- Guinea pigs, rats and baboons can be infected experimentally.[36]
- LCMV can be a contaminant of transplantable tumours.[27,28] Continuous cell lines may also be virus carriers, e.g. neuroblastoma[18] and baby hamster kidney cells (BHK-21).

Properties

- LCMV is a rodent borne single-stranded RNA virus that belongs to the Arenaviridae.[39,40]
- Different strains of LCMV have been isolated: strains Armstrong, Traub and WE in the early 1930s in the USA[41], strains OQ28 and BRC decades later.[42] Additional strains were identified in *Mus musculus*.[43]
- Different LCMV strains possess different virulences for guinea pig and hamster strains[25,26] as well as neonatal rats.[44]
- LCMV is transferred from natural hosts to others by contact with saliva, nasal secretions, or urine.[45,46]

- In natural infections of immunocompetent animals, virus is only shed by hamsters and mice infected prior to weaning.[45-48]
- Among enzootic infected populations of mice, the most common route of transmission is congenital in utero.[45-47]

Susceptibility

- Laboratory mouse strains (e.g. SWR/J, DBA/2, C57Bl/6, CBA/J) differ greatly in susceptibility to infection with different LCMV strains.[49]
- Laboratory rats and wild rats are not affected by natural LCMV infection.[19-21,50]
- Many laboratory rodents can experimentally be infected by LCMV, e.g. guinea pigs.[51] and rats.[52]

Organotropism

- Kidney
- Liver
- Brain[53]
- Salivary glands
- Lymphohaematopoetic system[38]
- Involvement of spleen, lymph nodes, adrenal glands, intestine, pancreas, and central nervous system is variable[35]

Clinical disease

- Natural infections in mice and hamsters can be perinatal persistent infections with late onset disease (or chronic immune complex disease): wasting at 7-10 months of age.[33,48]
- LCMV causes a lifelong symptomless infection in mice.[45,46]
- In humans, LCMV induces febrile illness, influenza-like symptoms[1], sensorineural deafness, labyrinth damage and meningeal involvement.[54]
- Clinical disease after experimental infection is influenced by the route of inoculation: parenteral inoculation induces visceral form in mice with asymptotic conjunctivitis, ascites, and somnolence.[53,55]
- Intracerebral inoculation produces lymphocytic choriomeningitis[45,46] and autoimmune haemolytic anaemia in different strains of mice.[56]
- In adult mice, some LCMV strains infiltrate splenic white pulp, ablate cytotxic T-lymphocyte response and produce persistent infection, while other genetically closely related strains do not.[57]
- In newborn rats, different LCMV strains induce diseases with various pathology in spleen and brain, individual behavioral deficits, several neuropathologies in the cerebellum and different immune responses to infection.[44]
- In rhesus macaques, the WE strain of LCMV causes a fatal hepatitis, while the Armstrong strain causes no disease.[58]

Pathology

- Natural infection in mice and hamsters:
  - Perinatal: antigen-antibody-immune-complex glomerulonephritis at the age of 7-10 months

  - Chronic disease: inflammatory lesions in many organs like glomerulonephritis, focal hepatic necrosis and disseminated lymphoid infiltrations in several body tissues[53,55]
- Experimental infection: T-cell mediated immune disease:
  - Murine hepatitis[59,60]
  - Lesions in the urinary tract: urolithiasis, hydronephrosis, cystitis and pyelonephritis[61] in Lewis rats after intracerebral injection
  - Liver degeneration (necrosis and inflammation), involvement of spleen, lymph nodes, adrenal glands, intestine, pancreas and central nervous system in marmosets and tamarins. LCMV antigens are isolated from necrotic foci and in non-degenerated organs like lung, kidney, urinary bladder, brain and testis.[35]

Morbidity and mortality

- LCMV strain ARM is avirulent for different hamster strains and guinea pigs.[25,62]
- LCMV strain WE causes 100% mortality[63] respectively high morbidity in guinea pigs[51] and high morbidity in inbred Syrian gold hamsters.[26]
- Naturally infection of mice and hamsters: high rate of infection, low rate of morbidity[45,46]
- *Foxn1^{nu}* mice without T-Lymphocytes develop high virus levels without morbidity like hepatitis and glomerulonephritis after intracerebral or intraperitoneal inoculation.[59,64-66]
- Morbidity and mortality in experimental infections depend on the way of infection, host species and age. Intracerebral infection of mice: 60-100% morbidity, 40-100% mortality; intraperitoneal infection of mice: 60% morbidity, no mortality[45,46]

Zoonotic potential

- Among 713 hospitalized patients with encephalitis 8% were associated with LCMV.[67]
- Wild mice are the natural reservoir of infection.[11,68]
- Golden hamster supplanted house mice as the major source of LCMV infection and transmit the virus to humans.[48,69,70]
- Many human cases of LCMV infection are described.[71-73]
- Human infections with LCMV arise from contact with infected animals, human to human congenital infection,[74,75] infection by transplantation of organs[76-78] or infection after needle stick injury.[79]
- Most human LCMV infections are linked to pet rodents and inhalation (aerosol, droplets), fomites, direct contact with excreta, blood, saliva.[1]
- LCMV infection of laboratory workers is associated with lab animals,[50,80] cultured tissues from infected mice or hamsters.
- Congenital LCMV infection in humans has been described in Europe in 1955**[74]** and in the USA in 1993.[75,81]
- LCMV has a teratogenic effect in the case of congenital infection in humans and is strongly neurotropic in the human fetus.[82]
- LCMV can cross the placenta, infect the developing fetus and induces severe and permanent injury.[83]

Interference with research

- Animals that carry LCMV are generally not suitable for experiments.

- The most important impact associated with an LCMV-infected colony is the potential infection of workers.

Oncology

- LCMV influences experimental oncology, enhances the frequency of lymphoma after treatment with carcinogen.[3]
- LCMV enhances the susceptibility for transplantable tumor cell lines.[84]
- LCMV enhances the survival time of leukemia-transplanted guinea pigs.[85]
- LCMV can enhance the incidence of lymphomas and can decrease the incidence of mammary tumors in mice.[86]

Teratology

- No data

Infectiology / Interactions with other infectious agents

- Interference with Rauscher virus: decreased incidence of leukaemia in mice.[87]

Immunology

- LCMV influences humoral and cellular immune responses.[88]
- LCMV causes a long-lasting immunodepression with decrease of proliferation capacity of splenic T-lymphocytes.[89-93]
- LCMV induces polyclonal cytotoxic T-lymphocyte stimulation.[94,95]
- Neonatally or congenitally infected mice have a lifelong chronic LCMV infection[96] and viraemia.[97,]
- LCMV enhances interleukin 12-mediated immunotoxicities.[99,100]
- LCMV induces different expression of alpha/beta interferons.[101]
- LCMV induces a transient bone marrow aplasia.[102]

Toxicology

- No data

Physiology

- Growth hormone deficiency, reduced weight and serum glucose levels can occur in different mice strains.[103,104]

Cell biology

- No data

Assisted reproductive technology

- No data

Special considerations

- The history of LCMV correlates with the development of modern immunology.[105,106]
- LCMV infection is an important model for immunological research. Several key concepts have been discovered: persistent viral infection,[45,46,107] MHC restriction,[108,109]

T cell memory and T cell exhaustion,[110] key role of immune pathology in disease,[105,106,111] discovery of mechanisms of immuntolerance.[112]

- In 1996 Nobel prizes were awarded to Peter Doherty and Rolf Zinkernagel who used LCMV as a model to enumerate the immunobiology of virus persistence and differential immune responses based on modes of transmission.[16]

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