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Gesellschaft für Versuchstierkunde
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Expert Information

From the Working Group on Hygiene

Implication of infectious agents on results of animal experiments

Kilham Rat Virus

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Contents

Kilham Rat Virus (KRV)

Background

- First described by Kilham and Olivier in 1959.[1]
- Belongs to the family Parvoviridae[2]
- Synonymous with Rat Virus (RV) and parvovirus r-1[2]
- Single stranded (ss) DNA-virus[2,3]
- Virion non-enveloped[2]

Prevalence

- Prevalence (serological) was high in rat colonies; although only few outbreaks of disease were reported; therefore, KRV was considered a significant pathogen.[2]
- A serological survey of laboratory rats in Western Europe facilities in 2009 resulted in a prevalence of parvoviruses in rats of 12.1.%, of which Kilham Rat Virus was present with 12.45%.[4]
- Another survey of more than 80'000 serological rat samples from North America and Europe over several years reported in 2009 a prevalence of KRV of 1.30% in total (1.23% North America, 4.05% Europe).[5]
- In Argentina, a serological prevalence of KRV was detected between 27.8 and 75% in conventional animal facilities.[6]

Host species

- Wild and laboratory rats are the natural hosts of the virus.[2,3]

Properties

- Transmission primarily via horizontal route through direct contact or fomites[2,3]
- Virus is shed via urine, faeces, milk and nasal secretions[2,3]; transmission via milk seems not to produce lethal doses for offspring.[7]
- Efficiency of transmission depends on strain of virus and age of rats at timepoint of infection.[2]
- Transplacental transmission was suggested but remains questionable[2,3], although in utero infection was shown through litter exchange experiments by Novotny and Hetrick.[7]
- Experimental transmission is possible via oronasal route in juvenile (4 weeks) and infant (2 days) rats and leads to infection.[8]
- Virus may persist for varying times after natural and experimental infection, the longer the earlier in life infection occurs.[3,8,9,10,11,12]
- Persistent infection is also described in athymic or T cell-deficient rats.[3,12,13]
- Can cause persistent infection of cell lines and transplantable tumours; transmission through contaminated cells and tumours is an important route of infection.[2]
- Resistant to environmental conditions (such as high temperature; infectivity retained after heating at 80°C for 2hr or 40°C for 60d, resistant to dessication, pH 2-11, chloroform, ether, alcohol)[2,14,15,16,17]

Susceptibility

- Wild and laboratory rats
- No strain-dependent susceptibility described[18]
- Syrian hamsters and other species such as *Mastomys natalensis* have shown to be susceptible to experimental infection.[2,19,20]
- Susceptibility greatest *in utero* and in first few days of live; most often results in neonatal loss[3]

Organotropism

- Viral replication only in mitotically active tissues [21] such as embryo, intestines, tumours
- Especially proliferating and growing tissues are affected; infection leads to cell destruction.[2]
- Predilection for the developing liver and cerebellum[22,23]

Clinical disease

- Most infections are subclinical and asymptomatic[3,24,25]; clinical disease is a rare event[2,3]; highly dependent on age at infection.[3]
- Infection can be severe or lethal, especially in athymic infant rats.[26]
- Cases of spontaneous clinical disease with deaths have been reported.[22,27]
- Major effects expected in the fetal development and early life.[2]
- Fetal deaths and teratologic effects; neonatal abnormalities have been attributed to KRV.[2,28]
- In pregnant rats increased uterine resorption was observed; with runting, ataxia, cerebellar hypoplasia and jaundice in the litter.[2]
- Severe disease of rats from birth to several weeks of age (with symptoms such as cerebellar hypoplasia, jaundice, furthermore haemorrhagic infarction with thrombosis in multiple organs incl. brain, spinal cord, testes, epididymidis) observed after natural infection with KRV.[2]
- Scrotal cyanosis, abdominal swelling, dehydration, other signs of severe illness can occur in juvenile and few weeks old male rats.[2]
- KRV is known to induce autoimmune diabetes in rats.[3]
- Cerebellar hypoplasia and ataxia in hamsters after experimental infection[29]
- Periodontal disease in hamsters[2]

Pathology

- Focal necrosis, haemorrhage, infarction[3]
- Haemorrhage and infarction especially in the central nervous system[23,30,31,32]
- Haemorrhagic encephalopathy reported in adult LEW rats after natural infection[2]
- Intranuclear parvoviral inclusions in areas of necrosis in clinically affected rats[3,33]
- Amphophilic intranuclear inclusions in endothelium and other cells of infected organs; focal necrosis, hypertrophy, vascular degeneration of hepatocytes, cholangitis, biliary hyperplasia in the liver[2]
- Increased leukocyte adhesion in the aortic epithelium[34]
- Mongoloid-type deformity in new-born hamsters after experimental infection[35]
- Cerebellar lesions in cats after experimental infection[36]

Morbidity and mortality

- When rats are newly infected during pregnancy, transmission to progeny is possible and may result in persistent infection of offspring.[37]
- According to Novotny and Hetrick, experimental infection of females during pregnancy results in up to 100% mortality of the offspring.[7]
- In contrast, when already persistently infected rats are getting pregnant (infection was before pregnancy) they do not produce infected progeny and no mortality was observed after experimental infection of offspring at day 0 or 1.[7,37]
- Progeny protected from infection presumably by maternal antibodies[37]
- Transmission of immunity from mother to offspring may lead to latent infections in young rats and support spreading of infection in rat populations.[7]
- Acute disease in hamsters after experimental infection[19]

Zoonotic potential

- Not described

Interference with research

Oncology

- Contamination of transplantable or chemically induced tumours[1,38,39,40]
- Contamination of leukaemias or leukaemia virus preparations[41,42,43]
- Suppression of leukaemia induction by Moloney virus[44]

Teratology

- Congenital malformation[45]
- Death and resorption of foetuses[22]

Infectiology / Interactions with other infectious agents

- Necrosis in the lung may support secondary colonisation with other microorganisms such as *Pasteurella pneumotropica.*[46]
- KRV together with H-1 and *Clostridium piliforme* can influence the prevalence rate of *Yersinia*-induced arthritis in rats.[47,48]

Immunology

- Infection of T and B lymphocytes and suppression of various lymphocyte functions[49]
- Stimulates autoreactive T lymphocytes specific for pancreatic antigens[50]
- Can cause acute autoimmune diabetes[3] or alter susceptibility to autoimmune diabetes in rat strains which are normally resistant to this syndrome (e.g. BB/Wor, LEW1.WR1)[51,52,53]
- Alters cytotoxic lymphocyte activity[54]
- Depresses lymphocyte viability and a variety of T cell functions like *in vitro* lymphoproliferative responses[38,39]
- Stimulates interferon production[55]

Toxicology

- No data

Physiology

- Inhibition of lipid formation in rat kidney cells *in vitro*[56]
- Increased abortion rate[57]

Cell biology

- Contaminant of cell lines[58]
- Persistent infection of cell lines and transplantable tumours[2,59,60]

Assisted reproductive technology

- No data

Special considerations

- No medical treatment described

Actualized by Christina Simon, Basel, December 2021

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