Flavivirus (Infection with) (causing louping Ill)

AETIOLOGY

Classification of the causative agent

Louping ill virus (LIV) is an arboviral flavivirus (enveloped, positive-sense single-stranded RNA) that is of most significance to sheep and red grouse (*Lagopus lagopus scoticus*). However, this virus has been shown to infect many species, and while wildlife are not believed to develop severe clinical signs secondary to infection, they likely play a role in disease persistence by acting as maintenance hosts. LIV is composed of multiple subtypes that tend to cluster geographically (e.g., Spanish, Turkish, British, Irish). LIV is closely related to tickborne encephalitis virus (TBEV), from which it is often clinically indistinguishable due to similarities in disease presentation. LIV is a zoonotic agent, although disease is less severe in humans.

Resistance to physical and chemical action

Temperature:	Not well determined; believed to be heat-sensitive
pH:	Not well determined
Chemicals/Disinfectants:	Susceptible to most commercial disinfectants
Survival:	Not well determined; believed to have poor environmental stability

EPIDEMIOLOGY

Hosts

- Sheep (*Ovis aries*)
- Red grouse (*Lagopus lagopus scoticus*)
- Blue hare/mountain hares (*Lepus timidus*)
- Goats (*Capra aegagrus hircus*)
- Red deer (*Cervus elaphus*) and roe deer (*Capreolus capreolus*)
- Humans (*Homo sapiens*)
- Many other species have demonstrated antibody responses or low levels of circulating virus in blood; it is not believed these species are significantly involved in disease transmission or maintenance, but this is still an active area of research.
    - Horses (*Equus ferus caballus*)
    - Cattle (*Bos taurus*)
    - Llamas (*Lama glama*)
    - Alpaca (*Vicugna pacos*)
    - European elk (*Alces alces*)
    - Pigs (*Sus scrofa*)
    - Badgers (*Meles meles*)
    - Rodents
        - European shrews (*Sorex* spp.)
        - Rats (*Rattus* spp.)
        - Voles (family *Cricetidae*, subfamily *Arvicolinae*)
        - Wood mice (*Apodemus sylvaticus*)
        - Some rodent species demonstrate susceptibility to disease in a laboratory setting, but the ecological relevance of this is uncertain
    - European rabbits (*Oryctolagus cuniculus*)
    - Dogs (*Canis famililaris*)

- There is experimental evidence to suggest ptarmigans (*Lagopus mutus*) and willow grouse (*L. lagopus*) are susceptible to disease

Vectors

- *Ixodes ricinus,*
- *I. persulcatus*
- *Rhipicephalus appendiculatus*
- *Haemaphysalis anatolicus*

Transmission

- Haematophagous ticks (vector-borne)
- *Ixodes ricinus* ticks are capable of transstadial, but not transovarial, transmission
- Co-feeding of ticks on non-viraemic hosts (especially mountain hares)
- Ingestion of infected ticks (grouse)
- Lambs and kids may become infected with LIV when they nurse, but this is likely not a significant route of transmission
- There is documentation of pigs becoming infected via consumption of raw, infectious lamb meat

Sources

- All species may become infected with the virus through contact with questing ticks
    - Only sheep and red grouse are believed to develop sufficient circulating viral titres for transmission
- Infected ticks
- Goat and sheep milk

Occurrence

LIV is present predominantly in the British Isles, Bulgaria, Turkey, and on the Iberian Peninsula, where *Ixodes ricinus* is commonly found. However, LIV is genetically similar to other tickborne viruses such as TBEV and is often clinically indistinguishable without diagnostic testing; therefore, the geographic range of LIV may be wider than what is currently appreciated.

Disease is most common in the spring, summer, and early fall when tick activity and questing is at its peak. *I. ricinus* is capable of overwintering, as its 3-stage life cycle demands, and will harbor the virus transstadially.

Currently, only sheep and grouse are believed to play a significant role in LIV maintenance. Other hosts are believed to be accidental and almost always fail to develop a viraemia suitable for transmission.

DIAGNOSIS

The incubation period of LIV in sheep is 6-18 days, and parenterally inoculated grouse develop clinical signs in 2-8 days.

Most sheep with neurologic signs die and case fatality rates average at approximately fifty percent. If an individual survives, they are protected from reinfection but often have permanent neurologic deficits. In endemic areas, clinical disease is typically more mild or subclinical, and mortality rates are significantly lower (5-10% versus 60% in naïve areas). Death tends to occur in animals less than 2 years of age, however, lambs are typically protected by maternal antibodies. Mortality in grouse has reached 80% in experimental settings.

Clinical diagnosis

Disease in sheep is characterised by a prolonged viraemia and biphasic fever. Initially, individuals are depressed and anorexic. The second febrile peak corresponds with the development of neurological signs and encephalitis, which often manifest as ataxia, incoordination, hyperexcitability, paralysis or paresis, torticollis, muscle tremors, salivation, nervous nibbling, head pressing, posterior paralysis, recumbency, torticollis, convulsions, coma, and death. The virus earned its name from the peculiar “louping gait” ataxic sheep develop.

Affected grouse become depressed and anorectic. Clinical signs are often vague, and obvious central nervous system deficits are lacking. Birds may also regurgitate crop contents and develop muscle weakness. Generally, the prognosis for survival is poor, especially for chicks. Large mortality events of wild red grouse due to LIV have been documented.

Lesions

- Gross lesions are typically not observed in the central nervous system of affected animals
    - Meningeal congestion may be seen in some individuals
- Mild neuronal degeneration with nonsuppurative meningoencephalitis and myelitis
    - Sheep: most prominent in the hindbrain and ventral horn of the spinal cord
    - Red grouse: most prominent in the cerebrum and optic lobes
- Gliosis
- Perivascular cuffing
- LIV is commonly associated with a secondary pneumonia

Differential diagnoses

- Chemical toxin exposure
- Sheep
    - Pregnancy toxaemia, hypocalcaemia
    - Maedi-Visna virus
    - Rabies virus
    - Listeriosis
    - Scrapie
- Red grouse
    - West Nile virus
    - Virulent Newcastle disease
    - High pathogenicity avian influenza

Laboratory diagnosis

Samples

For isolation of agent

- Uncoagulated peripheral blood (antemortem)
- Brain
- Cervical spinal cord

Serological tests

- Uncoagulated peripheral blood

Procedures

Identification of the agent

- Virus isolation via cell culture or intracerebral inoculation of suckling mice
- Immunohistochemistry (IHC)
- Reverse transcriptase polymerase chain reaction (RT-PCR)

Serological tests

- Haemagglutination inhibition (HI)
- Serum neutralisation assays
- Antibody-capture enzyme-linked immunosorbent assay (ELISA)
- Complement fixation
- Paired acute and convalescent sera for antibody titres
- Take caution when interpreting results, as cross-reactivity may occur with other flaviviruses

PREVENTION AND CONTROL

Sanitary prophylaxis

- Tick control methods should be exercised to prevent exposure (e.g., pasture rotation, destruction of habitat favorable to ticks, etc.)

Medical prophylaxis

- An inactivated vaccine has historically been used for sheep, goats, and cattle, but is no longer available
- A Semliki Forest virus recombinant vaccine is currently in development
- Acaricides are among the most commonly utilised tools for tick control in captive settings; this may not be feasible for wild animal species, however,
    - Acaricide wing tags and pour-on solutions have been used for captive red grouse populations with varying degrees of success
    - While deer are not believed to be significant reservoirs of LIV, they are a critical host species for *I. ricinus* ticks and play an important role in maintaining these ticks in the environment. Models suggest that acaricide treatment in areas where deer density is low may be effective in reducing tick burdens and therefore LIV prevalence.
- If LIV is newly introduced to a region, culling practices, quarantines, movement restrictions, and tick control should be implemented expediently; eradication becomes significantly more difficult once LIV is established in a tick population
- Mathematical models suggest culling of mountain hares is not an effective means of controlling LIV transmission if there are other host species, such as deer, present.

POTENTIAL IMPACTS OF DISEASE AGENT BEYOND CLINICAL ILLNESS

Risks to public health

- LIV is a zoonotic disease characterised by meningoencephalitis and a 4-10 day biphasic fever with influenza-like signs. Disease is typically self-limiting.
    - Currently, disease in humans is most commonly associated with those for whom LIV infection is an occupational hazard (e.g., veterinarians, abattoir workers, sheep farmers, laboratory staff).
    - Exposure of open skin wounds and aerosol inhalation are two notable transmission routes for human exposure, although there is concern regarding ingestion of unpasteurized goats' milk.

Risks to agriculture

- LIV infection in domestic sheep herds and grouse flocks can cause significant economic loss by means of widespread mortality.

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The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Science Department (scientific.dept@oie.int). Last updated 2020. Written by Samantha Gieger and Erin Furmaga with assistance from the USGS National Wildlife Health Center.