EUROPEAN BROWN HARE SYNDROME VIRUS

AETIOLOGY

Classification of the causative agent

European brown hare syndrome virus (EBHSV) is an enveloped, positive-sense single-stranded RNA calicivirus within the genus *Lagovirus*. Rabbit haemorrhagic disease virus (RHDV) is also classified in this genus and is a significant and common differential diagnosis. These two viruses are closely related genetically and antigenically but are somewhat disparate from other caliciviruses. There appear to be multiple strains of EBHSV, some of which are geographically limited to different parts of Europe.

EBHSV affects both free-ranging and farmed hares, and is characterized by acute necrotising hepatitis. Disease is fairly prevalent in Europe because the virus is easily transmitted between individuals and is extremely resilient in the environment.

Resistance to physical and chemical action

The following information is generally not well determined for EBHSV specifically, but is extrapolated from what is known about RHDV.

Temperature: Survives heat of 50°C for 1 hour; tolerates freeze-thaw cycles

pH: Stable at pH 4.5-10.5; inactivated at pH>12

Chemicals/Disinfectants: 0.5% sodium hypochlorite, substituted phenolics, 1% sodium hydroxide, 1-2% formalin

Survival: Extremely hardy when protected by organic material; can persist for months in decomposing rabbit carcasses

EPIDEMIOLOGY

Hosts

- European brown hares (*Lepus europaeus*)
- Northern hares (*Lepus timidus*)
- Eastern cottontail rabbits (*Sylvilagus floridanus*) may be a spillover/dead end host

Transmission

- Faecal-oral routes
- Inhalation of aerosols or respiratory droplets
- Direct hare-to-hare transmission

Sources

- Other infected hares
- Fomites, including arthropods as mechanical vectors
- Aerosols
- Faeces from infected hare

Occurrence

The presence of EBHS virus is believed to be geographically limited by the distribution of northern and European brown hares; most European countries have observed clinical cases. EBHSV has been detected in the Buenos Aires province of Argentina, most likely due to the importation of European brown hares and subsequent release in Santa Fé province in 1888.

Introduction of EHBSV to a naïve population can cause widely variable mortality rates, ranging from 10-100% in captivity. Most individuals in populations where the virus is endemic develop sufficient antibody responses and immunity, therefore, mortality rates are low.

Antibodies are assumed to be conferred to neonates via colostrum or transplacental passive transfer. Hares that survive clinical disease remain protected against re-infection due to long-lasting antibody responses.

Clinical disease has not been documented in hares less than 50 days of age, and infections are typically subclinical in individuals younger than 2-3 months of age. Mortality appears most significant in the fall when population density increases and weaned offspring become immunologically vulnerable.

For more recent, detailed information on the occurrence of this disease worldwide, see the OIE World Animal Health Information System - Wild (WAHIS-Wild) Interface [http://www.oie.int/wahis_2/public/wahidwild.php/Index].

DIAGNOSIS

Death in acutely affected free-ranging hares typically occurs in 2-7 days, but time to mortality may be prolonged up to 2 weeks in captive populations. While the liver is the target organ of the virus, macrophages become a significant source of virus after 3-4 days.

Viral antigen is sometimes identifiable in the livers of hares with chronic hepatitis, which indicates viral persistence and/or chronic disease states are possible.

Clinical diagnosis

Disease is typically peracute and animals often die before clinical signs are observed. Acutely affected hares are commonly anorexic and depressed. Abnormal behavior and neurologic signs are common and are likely sequelae of hepatic encephalopathy; there are descriptions of “crazy hares” that circle and maintain abnormal postures. It is common for affected wild hares to lose their fear of people and dogs. Death is often secondary to hepatic insufficiency and necrosis. Hunters often report seeing large groups of dead hares in the fall, and these sightings are typically at consistent geographic locations between years.

If disease progression is slow, individuals can develop icterus and signs of chronic hepatitis. Emaciation or otherwise poor body condition are also common with chronic disease.

Due to their genetic and antigenic relatedness and similarities in the laboratory environment, EBHSV is often assumed to behave similarly to RHDV *in vivo*. Hares in a compatible geographic location displaying neurologic signs and abnormal behavior are often presumptively diagnosed with EBHSV. Definitive diagnosis requires histopathology and identification of the virus.

Lesions

- If death was acute, gross lesions are often subtle or absent
- Hepatocellular necrosis
    - Single cell necrosis in periportal areas is characteristic
    - May also affect midzonal areas or entire lobules
    - Cells often exhibit mitochondrial mineralization
    - Accentuated lobular pattern

- Hepatic lipidosis and pallor; microscopic evidence of fatty change is common
- Hepatic fibrosis (chronic cases)
- Tubular necrosis and mineralisation
- Haemorrhage
    - Dark red tracheal and nasal mucosa
    - Pulmonary edema and/or petechial haemorrhage
    - Petechiae on serosal surfaces
    - May progress to disseminated intravascular coagulation, but occurs less frequently than in rabbits with RHD
- Inflammatory infiltrates range in significance with chronicity of disease
    - Portal infiltration by macrophages, lymphocytes, heterophils
    - Parenchymal infiltration by granulocytes
- Splenic and/or renal congestion and enlargement
- Icterus
- Infrequently, mucoid colitis or blood-stained intestinal content
- May see changes in other organs secondary to haemorrhage and circulatory failure

Differential diagnoses

- Rabbit haemorrhagic disease (RHD)
- Acute bacterial infections/septicaemia
    - Pseudotuberculosis
    - Tularemia
    - Pasteurellosis
    - Listeriosis
- Toxoplasmosis
- Meningitis/encephalitis
- Vestibular disease
- Toxin ingestion (e.g., anticoagulant rodenticide)

Laboratory diagnosis

Samples

For isolation of agent

- Liver
- Spleen
- Peripheral blood mononuclear cells
- Lung is suitable for histopathology

Serological tests

- Whole blood
- Serum

Procedures

Identification of the agent

- Immunohistochemistry (IHC)
- Haemagglutination assays (HA)
- Multiple enzyme-linked immunosorbent assays (ELISAs) are available
- Electron microscopy
    - Both negative-staining and immune modalities are utilised
- Reverse transcriptase polymerase chain reaction (RT-PCR)
- Agglutination of human type “A” or “O” red blood cells at pH 6.4 and at 4°C

Serological tests

- Haemagglutination inhibition (HI)
- Antibody and antigen capture ELISA

PREVENTION AND CONTROL

Sanitary prophylaxis

- Install adequate fencing and other distancing measures on hare farms to prevent interaction with wild free-ranging animals
- New additions to any captive hare population should be quarantined and serologically tested before introduction
- Exercise good biosecurity measures by decontaminating and/or changing shoes and clothing upon entering and exiting captive facilities to prevent introduction or carriage of infectious particles
    - The same principles are applicable to individuals and groups working with or near free-ranging hares: decontaminate and isolate soiled materials (including clothing and shoes) upon leaving an endemic area and utilise designated clean materials only in naïve areas.
    - Decontamination of vehicles is also recommended.
- Arthropod control may mitigate some disease transmission from wild hares to captive populations due to their potential role as mechanical vectors of virus
- Do not feed grass or hay contaminated with wild hare excreta to captive hares.

Medical prophylaxis

- There are no commercially available vaccines for EBHSV, but autogenous killed vaccines are often used on farms when disease or mortality rates increase.
- Translocation of hares from infected to naïve areas is ill-advised due to the potential for rapid spread and high mortality. If movement of hares is necessary, quarantine and serologic testing is recommended first.
- There is some evidence that suggests an association between certain MHC class II alleles and clinical outcome. While more research should be performed to understand this relationship more completely, maintaining immunogenetic heterogeneity within captive populations may help maintain some degree of population-scale vigour in the face of infection.

POTENTIAL IMPACTS OF DISEASE AGENT BEYOND CLINICAL ILLNESS

Risks to public health

- There is no perceptible risk of EBHSV to the public due to its narrow host range.

Risks to agriculture

- Outbreaks of EBHSV in previously uninfected populations often cause mass mortality events that can approach local extirpation. In the short-term, this can be detrimental to hare farmers and hunters; economic strain and food scarcity are potential secondary effects for relevant parties. Exposed populations are expected to stabilise over time, but this process may take years.

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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.