FLAVIVIRUS (TICKBORNE ENCEPHALITIS)

AETIOLOGY

Classification of the causative agent

Tickborne encephalitis virus (TBEV) is an arboviral flavivirus (enveloped, positive-sense, single-stranded RNA) enzootic to Eurasia and Japan. There are five known subtypes: European (TBEV-Eu), Siberian (TBEV-Sib), Far Eastern (TBEV-Fe), Himalayan (TBEV-Him), and Baikalian (TBEV-Bkl). Historically, it has been referred to as “Russian spring summer encephalitis” in Russia and “Central European encephalitis” in Europe.

TBEV is closely related to Louping ill virus (LIV), from which it is often clinically indistinguishable due to similarities in disease presentation. It is also a zoonotic agent and infects thousands of people annually.

Resistance to physical and chemical action

Temperature: Remains viable after refrigeration at 8°C for 10 days; incubation at 55°C for 5 minutes is effective in a laboratory setting; inactivation by pasteurisation is variable by method and viral strain, but low-temperature long-time techniques are more successful than high-temperature short-time techniques

pH: Inactivated at pH 2-3

Chemicals/Disinfectants: Susceptible to 40% ethanol and methanol; inactivated by detergents

Survival: Increased environmental stability in milk; UV irradiation is suitable for inactivation of small volumes or quantities of virus

EPIDEMIOLOGY

Hosts

- Barbary macaques (*Macaca sylvanus*)
- Cattle (*Bos taurus*)
- Common shrew (*Sorex araneus*)
- Domestic dogs (*Canis lupus familiaris*)
- European mole (*Talpa europaea*)
- Foxes (*Vulpes* spp.)
- Goats (*Capra aegagrus hircus*)
- Himalayan marmots (*Marmota himalayana*)
- Horses (*Equus ferus caballus*)
- Humans (*Homo sapiens*)
- Mouflons (*Ovis orientalis*) and domestic sheep (*Ovis aries*)
- Red squirrel (*Sciurus vulgaris*)
- Roe deer (*Capreolus capreolus*)
- Southern white-breasted hedgehogs (*Erinaceus concolor*)
- Swine (*Sus scrofa*)
- Mice
    - Japanese field mice (*Apodemus speciosus* & *argenteus*)
    - Northern birch mice (*Sicista betulina*)
    - Striped field mice (*Apodemus agrarius*)
    - Wood mice (*Apodemus sylvaticus*)

    - Yellow-necked mice (*Apodemus flavicollis*)
- Voles
    - Bank voles (*Myodes glareolus*)
    - Common voles (*Microtus arvalis*)
    - European pine voles (*Microtus agrestis*)
    - Field voles (*Microtus subterraneus*)
    - Gray red-backed vole (*Myodes rufocans*)
    - Northern red-backed vole (*Myodes rutilus*)
    - Tundra voles (*Microtus oeconomus*)
- Birds
    - Buntings (*Emberiza* spp.)
    - Common starlings (*Sturnus vulgaris*)
    - Corncrakes (*Crex crex*)
    - Corvids (*Corvus* spp.) including carrion crows (*C. corone*) and western jackdaws (*C. monedula*)
    - Eurasian magpies (*Pica pica*)
    - Eurasian woodcocks (*Scolopax rusticola*)
    - Eurasian wrynecks (*Jynx torquilla*)
    - Finches
        - Bramblings (*Fringilla montifringilla*)
        - Common chaffinches (*Fringilla coelebs*)
        - Common redpolls (*Carduelis flammea*)
        - Red crossbills (*Loxia curvirostra*)
    - Hazel grouse (*Bonasa bonasia*)
    - House sparrow (*Passer domesticus*)
    - Red-backed shrikes (*Lanius collurio*)
    - Thrushes (*Turdus* spp.), including redwings (*T. iliacus*) and fieldfares (*T. pilaris*)
    - Tree pipits (*Anthus trivialis*)
    - Waterfowl
        - Eurasian coots (*Fulica atra*)
        - Garganey (*Anas querquedula*)
        - Long-tailed ducks (*Clangula hyemalis*)
        - Velvet scoters (*Melanitta fusca*)
    - Wagtails, including western yellow wagtails (*Motacilla flava*) and white wagtails (*M. alba*)

Transmission

- Haematophagous arthropods obtain and transmit the virus while feeding, and infection is maintained transstadially
    - Transovarial transmission is possible but is suspected to be less important
    - Co-feeding on a host can transmit TBEV between ticks in the absence of a viraemia or presence of humoral immunity; co-feeding is believed to be a significant route of transmission for TBEV
- Secreted in goat's, sheep's, and cow's milk
- Vertical transmission has been demonstrated in experimentally infected voles and their offspring
- Some avian species are believed to transmit TBEV transovarially

Sources

- Unpasteurised milk and other dairy products
- Ixodid ticks
    - The primary vectors of TBEV are the castor bean tick (*Ixodes ricinus*) and the taiga tick (*I. persculcatus*) in Europe and Asia, respectively; *I. arboricola, gibbosus, hexagonus,* & *ovatus* less commonly
    - *Dermacentor reticulatus; D. marginatus* & *silvarum* less commonly
    - *Haemaphysalis concinna; H. intermix, japonica, longicornis,* & *punctata* less commonly
    - *Hyalomma marginatum*

Occurrence

TBEV is a zoonotic agent of significant concern in endemic areas and is the most common viral cause of human central nervous system disease in much of Europe; thousands of cases are reported annually. Disease in animals is not believed to be significant, but there is interest in using animals (particularly livestock) as sentinels for TBEV in the environment. Generally, small mammals are the most important maintenance hosts for TBEV because they develop and maintain a viraemia. Larger mammals, birds, and reptiles generally support viral maintenance indirectly by hosting ticks rather than developing a robust viraemia.

TBEV exists in foci and is not evenly distributed throughout a tick population; these clusters are believed to be characterised by areas ranging from 500 square meters to a few square kilometers where the virus is maintained in rodents. Beyond this is a periphery, sometimes spanning one kilometer in diameter from the original focus, where the virus exists at a much lower prevalence. Typically, the virus is brought out of the central focus into the periphery via ticks feeding on larger mammals traversing an area. These foci behave independently from one another despite their close proximity.

Ixodes ricinus, the primary vector of TBEV in Europe, is primarily found in grasslands and deciduous forests with abundant undergrowth. However, it can also be found in public greenspaces within urban environments. An extensive study in Norway indicates the tick persists at altitudes below 155 meters and at latitudes below 66.1°N (no larvae were found beyond 65°N). TBEV prevalence in ticks is highly variable based on geographic region and climate, but is generally higher in adults than immature stages. TBEV incidence tends to correspond with seasonal tick activity, which is variable by region but is typically characterised by warm, wet weather.

Infection and distribution of TBEV among avian species is poorly understood, but it is known that tick burdens are associated with the amount of time an individual spends on the ground. Due to their capacity for flight, birds are capable of translocating ticks to areas they may not otherwise reach; barriers that prohibit the movement of terrestrial species often do not hinder birds. Because of this, there is concern regarding the geographic spread of TBEV. However, ixodid ticks do not remain attached to avian hosts for prolonged periods of time, and this decreases the likelihood of significant geographic dispersion.

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

The pathophysiology of TBEV is fairly understudied and inadequately understood. The threshold viral titer necessary for transmission to a feeding tick has not been determined. Bank voles experimentally inoculated subcutaneously with TBEV-Eu failed to develop neurologic disease, and specific neutralising antibodies were detected in serum at 28 days post inoculation. Data from the same study suggest viral RNA may be detected in blood as soon as 5 days post-inoculation and remain detectable 28 days post-inoculation. Serum may fail to yield detectable RNA sooner than whole blood.

Livestock do not commonly show clinical disease but can develop robust, long-lasting, and specific antibody responses to infection. Because of this, there is interest in using goats and sheep as sentinels for TBEV in an area. Some avian species are thought to develop a prolonged viraemia, but most of what is known is in regards to antibody titres from serosurveys.

Clinical diagnosis

Only one case of clinical TBEV infection in sheep has been documented: a five-month-old lamb from Bavaria, Germany developed acute fever, ataxia, and tremors before progressing to recumbency. The animal was humanely euthanised.

Not all dogs infected with TBEV develop clinical signs, but disease is typically characterised by fever, behavior changes, proprioceptive deficits, and central nervous system deficits such as motor deficits, central vestibular disease, and cranial nerve deficits. Dogs may die suddenly within days of infection. Generally, if the animal survives the first week of infection, prognosis is greatly improved.

Horses will be of ill-thrift and develop inappetence, ataxia, muscle cramping, and paralysis of the neck and forelimbs. Macaques develop clinical signs that resemble human infection: biphasic fever, lethargy, myalgia, nausea and vomiting, paresis or paralysis, hyperkinesia, tremors, convulsions, and potentially death.

Lesions

- Diffuse lymphohistiocytic and granulocytic meningoencephalitis with lymphocytic perivascular cuffing, neuronal degeneration and necrosis, and focal glial proliferation
- Lymphohistiocytic and mononuclear infiltration of leptomeninges
- Multiple regions of the brain and spinal cord are affected, grey matter more significantly than white matter

Differential diagnoses

- Louping-ill virus
- Listeriosis
- Borna disease virus
- West Nile virus
- Rabies

Laboratory diagnosis

Samples

For isolation of agent

- Serum, whole blood in EDTA
- Brain, spinal cord
- Cerebrospinal fluid

Serological tests

- Serum, whole blood in EDTA

Procedures

Identification of the agent

- Reverse-transcriptase polymerase chain reaction (RT-PCR)
- Virus isolation
- Immunohistochemistry (IHC)

Serological tests

- IgM- or IgG-capture enzyme-linked immunosorbent assay (ELISA)
    - Paired acute and convalescent sera for detecting seroconversion or rising titres
    - Positive ELISA assays should be confirmed with serum neutralisation assays
    - Cross-reactivity with other flaviviruses can occur
- Plaque reduction/serum neutralisation test
    - Considered the “gold standard” for detection

PREVENTION AND CONTROL

Sanitary prophylaxis

- Tick control methods should be exercised to prevent exposure (e.g., pasture rotation, destruction of habitat favorable to ticks, acaricide treatment, etc.).
- Rodent control may help decrease the number of feeding ticks brought into an area; rodent-proofing buildings, baiting, trapping, and destroying rodent dwellings or other suitable habitat near locations of human use can deter rodents.

Medical prophylaxis

- There are multiple vaccines available for human use
- An inactivated virus vaccine candidate used in sheep successfully induced production of TBEV-specific antibodies; no viraemia was detected after viral challenge nor was TBEV RNA detected in milk.
- Pasteurisation of dairy products (low-temperature long-time) is recommended to prevent alimentary infection in humans.
- Routine serologic screening of dairy herds or bulk-tank milk samples for TBEV in endemic areas may be a useful early detection tool.

POTENTIAL IMPACTS OF DISEASE AGENT BEYOND CLINICAL ILLNESS

Risks to public health

- TBEV is a zoonotic disease characterised by a biphasic meningoencephalitis, and is obtained from infected feeding ticks or ingesting unpasteurised dairy products from infected goats, sheep, and cattle.
- Infection may be considered an occupational hazard for some individuals, particularly those working in agriculture, horticulture, or forestry. There are data suggesting further education regarding effective tick prevention, tick-borne diseases, and available vaccines could reduce incidence in these groups.

Risks to agriculture

- Livestock do not typically develop disease after infection with TBEV, however, they can transmit the virus via their milk. This is a significant concern for the raw and unpasteurised dairy market, and contamination of product with TBEV can significantly impact its safety and saleability.

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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.