Viral Encephalitis Backgrounder

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Causative agent

The Eastern, Western, and Venezuelan Equine Encephalitis (EEE, WEE, and VEE, respectively) viruses are alphaviruses, and members of the Togaviridae family. Togaviruses are 70 nanometer (nm), enveloped viruses with a protein-coated nucleic acid core, and have 20 faces on their surface. These viruses contain positive-sense, single-stranded RNA. Although the EEE, WEE, and VEE viruses are serologically distinct, the WEE virus genome is closely related to the EEE virus genome. There are two clinically relevant variants of EEE (North American and South American). Although at least six subtypes of VEE have been recognized and named, only two subtypes are clinically important for equids or humans.

West Nile Virus (WNV) and Japanese Encephalitis Virus (JEV) are members of the Flaviviridae family. Flaviviruses are 40 to 70 nm, enveloped viruses with a shape similar to togaviruses. Like togaviruses, they contain positive-sense, single-stranded RNA.

Natural distribution

The EEE and WEE viruses can infect equids (e.g., horses, donkeys, mules), as well as pigeons, pheasants, quail, ratites (e.g., ostriches, emus), and humans. Bats, reptiles, amphibians, and forest-dwelling marsupials and rodents may also be infected and show no clinical signs of disease. Infection of swine with EEE virus has also been reported. The North American variant of EEE is typically found in the Caribbean, Texas, eastern Canadian provinces, and eastern United States. Cases have also been reported in Arkansas, Mississippi, Minnesota, South Dakota, and Texas. The South American variant of the virus is less pathogenic, and is found in Central and South America. WEE is found in the western Canadian provinces, Mexico, South America, and the western United States.

VEE affects equids and humans. Cattle, pigs, and dogs may also be infected, but may show no clinical signs of disease. The virus is found commonly in Central and South America, Mexico, Trinidad and, less frequently, in the southern United States (sylvatic or enzootic subtypes). The VEE virus was first identified in the 1930s in Venezuela. Although enzootic subtypes are found in Florida, the Rocky Mountains, and the northern plains of the United States, outbreaks are generally limited to northern and western South America and are caused by epizootic subtypes. The last outbreak in the United States of an epizootic subtype of VEE was in 1971.

WNV was first isolated in Uganda in 1937. WNV occurs in Asia, Europe, Africa, Australia, the Middle East, and North America. The first cases of WNV infection diagnosed in the United States were identified in 1999; by 2004, cases had been reported in 48 states (Hawaii and Alaska have reported no cases to date). Clinical WNV infection has been reported as developing in equids, humans, geese, and wild birds. Sheep, chickens, and swine can be experimentally infected with WNV.

JEV affects birds, bats, equids, swine, and humans. The virus is widespread in Asia; countries and regions currently affected by JEV include Japan, Cambodia, China, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Republic of Korea, Thailand, Vietnam, the southeastern Russian Federation, the Indian subcontinent, Papua New Guinea, and northeastern Australia.

Transmission

The principle vectors of EEE virus, WEE virus, WNV, and JEV are mosquitoes. The Rocky Mountain wood tick (*Dermacentor andersoni*) is also a vector of the WEE virus. Mosquitoes and other blood-sucking insects (including black flies) transmit VEE. *Culex pipiens* is the primary vector for WNV, and *Culex tritaenorrhynchus* is the primary vector for JEV. These viruses are frequently referred to as arboviruses, indicating that the viruses are primarily carried by birds and transmitted by mosquitoes

or ticks. Mosquitoes infected with the EEE and WEE viruses are capable of infecting their offspring; this is referred to as vertical transmission. Once introduced into a flock, bird-to-bird transmission of the EEE and WEE viruses can occur via feather picking and cannibalism.

Wild birds serve as amplifiers and reservoirs of the EEE, WEE, and VEE viruses. Small rodents may also serve as reservoirs of the EEE and VEE viruses. In tropical and sub-tropical climates, these viruses are endemic in a bird/rodent-mosquito cycle. The incubation period for the EEE, WEE, and VEE viruses in horses is 5-14 days.

Horses and humans are considered dead-end hosts for the EEE and WEE viruses; direct horse-to-horse or horse-to-human transmission does not occur. Unlike the EEE and WEE viruses, the VEE virus is shed in the oral and nasal secretions of infected animals, and transmission of disease may occur by direct contact or aerosolization; therefore, an infected equid is capable of infecting a susceptible animal or human. Equids with circulating VEE virus particles are capable of amplifying the virus and infecting others via insect vectors. Because mosquitoes and other blood-sucking insects transmit VEE virus, the potential for rapid spread of disease is higher than that associated with the EEE or WEE viruses.

Wild geese appear to be a natural host of WNV, but more than 300 species of birds can harbor and disseminate the virus. Migratory birds may play a primary role in introducing WNV into new areas. House sparrows, which are readily infected with WNV and develop high circulating concentrations of virus, are thought to be important in the spread of WNV. The incubation period for WNV disease is 7 to 14 days in horses and 3 to 14 days in humans. Humans and equids are considered dead-end hosts for WNV due to the low concentration of circulating virus particles associated with infection, and are not likely to serve as sources of disease transmission to other susceptible hosts. Rare human-to-human transmission of WNV has occurred via blood transfusions, organ transplants, and breastfeeding.

Herons and egrets are believed to be natural hosts for JEV. Pigs and birds are capable of acting as amplifying hosts due to high concentrations of circulating virus during infection. The incubation period for JEV disease is 4 to14 days in equids and 5 to 15 days in humans. Human-to-human or horse-to-horse transmission does not occur.

Because of the potential for human infection and rapid spread of these viruses, the World Organization for Animal Health (OIE) has classified EEE virus, WEE virus, VEE virus, WNV, and JEV as notifiable animal diseases. In recognition of the potential for use in bioterrorism, EEE virus, WEE virus, and VEE virus are classified as Category B agents by the Centers for Disease Control and Prevention (CDC). Although not currently classified as a notifiable disease by the OIE, the Agricultural Bioterrorism Act of 2002 recognized JEV as an agent that could pose a severe threat to animal health, animal and human health, or animal products in the United States. Fatal infections have developed in human laboratory workers handling samples of encephalitis viruses; therefore, it is recommended that laboratories follow biosafety level 3 protocols.

Clinical Signs

Clinical infections with EEE virus, WEE virus, VEE virus, WNV, and JEV are more commonly reported during summer and early fall, and coincide with high mosquito populations. Aged, young, and immunocompromised humans and animals are at higher risk of developing severe clinical signs.

Clinical signs usually develop within 7 days of infection with the EEE and WEE viruses. Affected equids exhibit fever, depression, anorexia, and variable, progressive neurologic signs. Neurologic signs may include behavioral changes, hyperexcitability, pharyngeal (throat) paralysis, head pressing, blindness, circling behavior, ataxia (incoordination), paralysis of the hind limbs or of all four limbs, recumbency, aggression, and seizures. Death can occur in 2 to 7 days. Following a 4 to 15 day incubation period, humans with EEE or WEE may exhibit symptoms that range from mild, flu-like signs to seizures, coma, and death. The EEE and WEE viruses can cause hemorrhagic enteritis in ratites.

Infection with the VEE virus results in encephalomyelitis (inflammation of the brain and spinal cord) less frequently than infection with the EEE and WEE viruses. VEE virus also damages blood vessels and organs. Affected equids exhibit high fever, wide stance, drooping lips, drooping ears, and sleepiness. They may be unable to swallow due to esophageal paralysis. Incoordination, weakness, circling, head pressing, blindness, deafness, hyperesthesia (increased sensitivity to touch, pressure, or pain), teeth grinding, aimless chewing, recumbency, seizures, and coma may be observed. Death may

occur in 5 to 14 days. Humans infected with the VEE virus may develop fever, intense headache, photophobia (increased sensitivity to light), muscle pain, chills, vomiting, diarrhea, convulsions, and other neurologic abnormalities. The incubation period for VEE virus in humans is 1 to 6 days.

Equids with WNV encephalitis have variable clinical signs that may closely resemble those observed with infection by the EEE, WEE, or VEE viruses. Affected animals may exhibit behavioral changes, incoordination, stumbling, depression or apprehension, weakness, inability to stand, focal muscle twitching, seizures, coma, or death. Fever is not a consistent sign of WNV disease.

Less than 1% of humans or animals infected with WNV develop clinical signs. Clinical signs may develop gradually or rapidly, and include high fever, sore throat, headache, neck stiffness, muscle or joint pain, focal facial muscle fasciculations, hyperesthesia, incoordination, difficulty eating and drinking, stumbling, weakness, dullness, fatigue, increased drowsiness, paralysis of one or more limbs, recumbency, and seizures.

Disease resulting from JEV infection in horses is clinically similar to that resulting from infection with the EEE, WEE, and VEE viruses, but is milder. Infection may also be inapparent. Three clinical syndromes have been described as resulting from JEV infection: transient, lethargic, and hyperexcitable. In the transient form, infected horses develop a fever accompanied by anorexia, sluggish movement, and congested or icteric (jaundiced) mucous membranes. Horses so affected usually recover. Horses with the lethargic form exhibit fever, lethargy, anorexia, nasal discharge, icterus (jaundice), petechia (pinpoint hemorrhages on the mucous membranes), incoordination, staggering, neck rigidity, radial nerve paralysis (resulting in an inability to advance and bear weight on the front limbs), and impaired vision. Recovery usually occurs in 4 to 5 days. In the hyperexcitable form, affected horses exhibit dementia, high fever, aimless wandering, visual impairment, fearfulness, violent behavior, blindness, profuse sweating, teeth grinding, and muscle twitching. This form is less common than the transient or lethargic forms of the disease, but is more likely to result in death in 24 to 48 hours. Humans with JEV commonly develop neurologic sequelae, such as psychiatric disturbances, deficits in physical movement, and catatonia. JEV infection may cause reproductive failure in swine.

Diagnosis

Because neurologic signs produced by EEE virus, WEE virus, VEE virus, and WNV are similar, differentiation of the causative agent is not possible on the basis of clinical signs. In addition, clinical signs of this disease may mimic those of rabies. Other causes of neurologic signs, including bacterial infection, trauma, tumors, and degenerative or developmental diseases, should be ruled out by use of proper diagnostics.

Prior vaccination may complicate the diagnosis of viral encephalitis; serologic assays are unable to differentiate vaccine-derived antibodies from those produced during natural infection. Definitive diagnosis of viral encephalitis is achieved via virus isolation. Polymerase chain reaction (PCR) detection of viral nucleic acids or demonstration of seroconversion may be diagnostic for infection in vaccinated horses. WEE virus is rarely isolated from infected horses, and VEE virus is infrequently isolated. The brain is the optimal tissue from which to obtain samples for virus isolation.

Acute (taken during febrile period) and convalescent (2 to 3 weeks later) blood serum samples can be submitted for evaluation by hemagglutination-inhibition, virus neutralization, complement fixation, or capture enzyme-linked immunosorbent assay (ELISA). Seroconversion, or a four-fold increase in antibody titers between acute and convalescent samples, is confirmatory for viral encephalitis. Positive single serum samples can be diagnostic in unvaccinated horses, but are of little value in confirming infection in vaccinated animals. Reverse transcriptase PCR is also available for diagnosis of EEE, WEE, and VEE. Cerebrospinal fluid (CSF), spinal tissue, or brain tissue can also be submitted for determination of antibody concentrations or PCR. Serum samples should be submitted in a red-topped or clot-separator tube, and CSF samples should be submitted in red-topped tubes.

Confirmation of infection with the EEE, WEE, or VEE viruses requires isolation and identification of the virus in cell culture or via mouse inoculation procedures. JEV infection can be confirmed via ovine cell culture or chicken embryo yolk sac isolation, PCR, or detection of seroconversion.

Treatment

EEE, WEE, VEE, and JEV encephalitis are reportable diseases in the United States. WNV encephalitis is reportable if cases are observed in a non-endemic area (i.e., in an area that has not previously had confirmed cases of WNV encephalitis). State or Federal animal health officials should be notified immediately when viral encephalitis is observed.

Treatment is primarily palliative, and supportive care is paramount to increasing the chance of survival. Steroids and/or nonsteroidal anti-inflammatories are frequently used to reduce inflammation, and antimicrobials may be needed for treatment of wounds and/or secondary bacterial infection. Anticonvulsive medication is indicated for animals that develop seizures. Intravenous fluids may be necessary to maintain hydration, and parenteral nutrition (IV feeding) or tube-feeding may be necessary for completely anorectic horses. Severely affected horses may need to be supported in a sling. Protection of the head and limbs from traumatic injury is also important. An immunoglobulin (antiserum) product has been licensed for use in the treatment of acute WNV disease in horses.

Horses that recover following viral encephalitic disease associated with moderate to severe neurologic signs often have residual abnormalities in their gait or behavior. Approximately 35% of humans that recover from EEE have mild to severe neurologic deficits.

Morbidity and Mortality

EEE virus causes the highest mortality of the alphaviruses; the case fatality rate (the percent of affected horses that die from disease) approaches 90% for equids and 30 to 50% for humans. WEE is milder than EEE, and its case fatality rate is approximately 20 to 30% for equids and 10% for humans. In ratites, morbidity and case fatality rates from hemorrhagic enteritis may exceed 85%. Morbidity and case fatality rates from WEE in pheasants and other susceptible birds can approach 90%.

The morbidity rate for VEE can approach 90%. Case fatality rates associated with VEE in equids range from 30 to 90%. VEE in humans is milder, with a case fatality rate of approximately 1%. However, humans are very susceptible to VEE, and morbidity rates approach 100% following exposure to the virus.

WNV infection in equids is associated with a 33% case fatality rate. Animals that recover are considered immune to subsequent infection, but potentially fatal relapses following apparent recovery have been observed, WNV infections in humans are associated with a 3 to 15% case fatality rate.

JEV infection in equids is associated with a 0 to 10% case fatality rate in endemic areas, but outbreaks have resulted in case fatality rates as high as 40%. The case fatality rate for JEV in humans can approach 60%, with 30% of survivors developing serious neurologic sequelae.

Prevention and Control

Because EEE, WEE, VEE, WNV, and JEV may produce clinical signs similar to those observed with rabies, extreme caution should be used when examining patients with neurologic signs. At minimum, protective gloves should be worn during handling of patients or collection and handling of tissue or fluid samples.

The EEE and WEE viruses do not survive outside of the host, but VEE virus may persist in dried blood and exudates. The EEE and WEE viruses are susceptible to moist or dry heat, dessication, and disinfection with 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, and formaldehyde solutions. WNV is susceptible to ultraviolet and gamma irradiation, heat, and disinfection with 3-8% formaldehyde, 2% glutaraldehyde, 2 to 3% hydrogen peroxide, 500 to 5000 ppm chlorine, 1% iodine, phenol iodophor, and organic solvent solutions. JEV is susceptible to heat, ultraviolet and gamma irradiation, and 70% ethanol, 2% glutaraldehyde, 3-8% formaldehyde, 1% sodium hypochlorite, iodine, phenol iodophor, and organic solvent solutions.

Inactivated vaccines against the EEE, WEE, and VEE viruses are available for horses; however, the VEE virus vaccine has limited efficacy due to the strains used for production of the vaccine. Vaccines against JEV virus are used in China and Japan, but are not available in the United States. Killed and recombinant vaccines are available for the prevention of WNV. In addition, the first DNA vaccine licensed for use in the United States is also available for prevention of WNV. Vaccination programs for protection against the viral encephalitides are largely based on the seasonality of mosquito populations; in

warmer climates, where mosquitoes may be present year-round, susceptible animals are vaccinated more frequently (2 to 4 times per year).

Strict mosquito control measures reduce the risk of exposure and subsequent disease. Elimination of standing water and other mosquito breeding sites is important. Use of fans, mosquito repellents, and insecticides may provide relief and reduce risk of exposure. Mosquito activity is higher from dusk until dawn; therefore, avoiding turning horses out to pasture and outdoor activities during that period reduces exposure.

Because VEE virus can be transmitted by contact or aerosol, isolation measures and protective clothing and equipment are recommended. Extreme caution should be used when handling patients, fluids, or tissues suspected or known to be infected.

JEV can be amplified in swine; therefore, reducing movement of swine may reduce transmission of JEV to susceptible animals. Horses, humans, and ruminants do not amplify the virus, and it is unnecessary to restrict movement of these species.