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Hendra Virus Infection

Equine Morbillivirus Pneumonia, Acute Equine Respiratory Syndrome

Last Updated: December 2015

Importance

Hendra virus infection is an emerging viral disease of horses and humans in Australia. Although this disease is uncommon, cases in horses have been reported with increasing frequency since it was first recognized in 1994. Hendra virus is maintained in asymptomatic flying foxes (pteropid fruit bats). Virus shedding from these bats appears to increase at unpredictable intervals, leading to spillover events that transmit Hendra virus to horses. Infected horses usually experience a brief, severe respiratory or neurological illness with a high case fatality rate, and are thought to be incidental hosts. Horse-to-horse transmission seems to be rare among animals kept on pastures, although infected horses brought into stables have spread the virus to a few animals in close contact. In some incidents, Hendra virus spread from horses to humans during close contact; human infections from other sources, including direct contact with flying foxes, have not been reported. Four of the seven clinical cases in humans were fatal. Other species may also be susceptible to Hendra virus. Infections without clinical signs have been reported rarely in dogs exposed to infected horses, and additional species, including cats, pigs, ferrets and pocket pets (hamsters, guinea pigs), can be infected experimentally. A vaccine was recently introduced for horses, but no vaccine or specific antiviral treatment has been found yet for humans. Uncertainty about the ability of Hendra virus to persist long-term has resulted in the euthanasia of infected horses and dogs in Australia even when the illness was not fatal.

Etiology

Hendra virus (HeV) is a member of the genus Henipavirus in the family Paramyxoviridae. This genus also includes Nipah virus, Cedar virus (an apparently nonpathogenic virus found in Australian bats) and additional uncharacterized henipaviruses in various locations. Multiple Hendra virus variants circulate in bats. Whether these viruses differ in virulence for other animals is unknown; however, several variants have been found in clinical cases in horses and humans.

Species Affected

Bats of the genus Pteropus (pteropid fruit bats/ flying foxes) appear to be the reservoir hosts. Hendra virus has been detected in all four species of Australian flying foxes: Pteropus alecto, P. poliocephalus, P. scapulatus and Pteropus conspicillatus. However, P. alecto and P. conspicillatus seem to be infected and/or shed virus more often than P. poliocephalus or P. scapulatus.

Other mammals are thought to be incidental hosts. All clinical cases in animals, to date, have occurred in horses, but other species may also be susceptible. In an early experimental study, Hendra virus was pathogenic in cats and guinea pigs, but mice, rats, two dogs, rabbits and chickens did not develop clinical signs. Definitive seroconversion was only observed in the rabbits in this study, although one dog and three of four rats had equivocal neutralizing titers. However, naturally acquired subclinical infections were later detected in two dogs on properties with sick horses, and an unpublished study has confirmed that dogs can be experimentally infected without clinical signs. Aged (one-year-old) mice are now known to be susceptible to intranasal inoculation, and develop clinical signs. Other species that have been experimentally infected with Hendra virus include pigs, ferrets, guinea pigs, hamsters and African green monkeys (Cercopithecus aethiops). As of 2015, naturally acquired infections have not been reported in any species other than horses and dogs.

Zoonotic potential

Humans are susceptible to Hendra virus. To date, all clinical cases have been acquired during close contact with infected horses and/or their tissues. Necropsies are a particularly high-risk procedure, but any contact with blood, secretions or tissues also carries a risk. At least one case is thought to have resulted from contact with nasal fluids from an asymptomatic horse (while performing nasal cavity lavage for another condition) during the incubation period. No one has apparently been infected by direct or indirect exposure to infected flying foxes, and surveys have found no evidence of Hendra virus infections among people who care for these animals.
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**Geographic Distribution**

Hendra virus infections have been seen only in Australia, where this virus is endemic in flying foxes. Seropositive flying foxes have been found from Darwin in north central Australia to Melbourne in southeastern Australia. Cases in horses have only been reported from eastern Australia, in the states of Queensland and New South Wales. Antibodies detected in flying foxes in Papua New Guinea might be caused by Hendra virus or a related virus.

Currently there is no evidence that Hendra virus exists in other areas. However, henipaviruses or antibodies to these viruses have been detected in bats on several continents. Most of these viruses are poorly characterized.

**Transmission**

In flying foxes, infectious virus and/or viral nucleic acids have been found in urine, blood, throat swabs, saliva, feces, fetal tissues and uterine fluids. Urine is currently thought to be the most important source of this virus, with other secretions and excretions (e.g., feces, nasal and oral secretions) probably less significant in transmission. Virus prevalence appears to wax and wane in bat populations, with periodic pulses of high virus shedding in bat urine. One such pulse lasted for 2-3 months. Vertical transmission has been demonstrated, although a recent survey of archived flying fox tissues suggests that it might not be common. Whether Hendra virus persists in local populations of flying foxes (with periodic recrudescence), is transmitted between groups, or is maintained by some combination of these processes is uncertain.

Horses are thought to become infected by ingesting or inhaling Hendra virus from the environment, most likely when they feed in areas contaminated by flying fox urine and/or virus-contaminated fruits and spats (fibrous plant material that remains after chewing by bats). The index case is usually a horse kept outside, near flying fox activity. Hendra virus does not appear to be highly contagious among horses, and close contact seems to be necessary for it to spread. Infected horses on pastures have rarely transmitted the virus to their companions. In two outbreaks, however, infected animals in stables spread the virus to several contacts. In horses, there is evidence for Hendra virus shedding in nasal and oral secretions, urine, feces, blood and a wide variety of tissues, although the presence of infectious virus has not been confirmed in all secretions/excretions (some investigations only detected viral nucleic acids). Hendra virus appears to be widespread in the body by the time clinical signs appear, and it has been found in nasal secretions before the onset of clinical signs. Whether horses can remain persistently infected after recovery from clinical signs is currently uncertain.

There is limited information about Hendra virus infections in other animals, but several species are susceptible to experimental inoculation by the intranasal or oronasal routes. Cats could be infected intranasally, orally and by subcutaneous inoculation. How two dogs became infected under natural conditions is unclear, but both lived on properties with infected horses, and one dog had probably had been exposed to the blood of a sick horse. Viral nucleic acids were detected in the blood and tissues of one naturally infected pet dog, although this animal did not transmit the virus to people or to two other dogs on the property. Some experimentally infected dogs shed infectious virus for a short time in respiratory secretions. Experimentally infected cats were able to transmit Hendra virus to other cats or horses in close contact. In this experiment, the virus was detected in feline urine, but not in nasal secretions, oral secretions or feces. In experimentally infected pigs, Hendra virus was found primarily in the respiratory tract; pigs shed infectious virus in oral and nasal secretions and feces, and viral RNA was also detected in ocular secretions, but there was no evidence of virus excretion in the urine.

Humans have been infected during close contact with sick horses and during necropsies, probably via body fluids or aerosols. Person-to-person transmission has not been seen, but Hendra virus has been isolated from nasopharyngeal secretions and the kidneys, and detected by PCR in patients’ urine. The virus may be shed for several weeks in acute cases. One person developed Hendra virus-associated neurological signs a year after infection, raising the possibility that this virus might persist in some body site(s) after recovery. A recent study found no evidence of long-term virus persistence in two survivors.

Transmission may be possible on fomites, particularly in closed environments such as stables. Under optimal laboratory conditions, Hendra virus survived for more than four days in flying fox urine at 22°C (72°F). This virus can also remain viable for a few hours to a few days (generally less than four days) in fruit juice or fruit. It does not survive well at higher temperatures, and it is inactivated in less than a day in either urine or fruit juice at 37°C (98.6°F). In one study, the half-life of this virus in cell culture medium was approximately 13 days at 4°C, 2 days at 22°C and 2 minutes at 56°C.

**Disinfection**

Like other paramyxoviruses, Hendra virus is expected to be susceptible to soaps, detergents and many common disinfectants including hypochlorite, iodophors, biguanidines (e.g. chlorhexidine), Virkon® and quaternary ammonium compounds. This virus is susceptible to desiccation or heat, but resists inactivation by acids or alkalis; it can survive a wide pH range from 4 to 11.

**Infections in Animals**

**Incubation Period**

In horses, the incubation period ranged from 3 to 16 days, and was slightly longer in natural cases (5-16 days).
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Other species

No clinical signs have been reported in naturally or experimentally infected dogs, with the possible exception of an episode of apparent discomfort in one animal. Despite the absence of clinical signs, this naturally infected dog had lesions at necropsy. The other naturally infected dog seroconverted with no evidence of virus replication. In experimentally infected cats, fever and increased respiratory rates were followed by severe illness and death within 24 hours. Experimentally infected pigs developed fever and depression. Some pigs also had respiratory signs (cough, respiratory distress), which were fatal in one severe case. One pig developed both respiratory signs and mild neurological signs, but recovered. Severe respiratory disease was seen in experimentally infected African green monkeys, while ferrets had a nonfatal illness with signs of fever, depression and generalized tremors. Some guinea pigs developed generalized, fatal vascular disease, with few clinical signs before death, while others had nonspecific signs (depression, anorexia) and recovered. Syrian golden hamsters (Mesocricetus auratus) had either fatal respiratory signs, or respiratory signs followed by neurological signs. Fatal illness with neurological signs (ataxia, muscle tremors) was also seen in one-year-old (aged) mice, while 2-month-old mice were resistant. Flying foxes (including pregnant animals) appear to remain asymptomatic, and all infected animals may not seroconvert.

Post Mortem Lesions

Necropsies have been linked to human cases, and should be performed only if they can be carried out safely, using recommended PPE and other precautions. Routine necropsy precautions may not be sufficient to protect people.

Horses

In horses with the respiratory syndrome, post–mortem lesions have been found mainly in the lower respiratory tract. Common lesions include marked pulmonary edema, dilation of the pulmonary lymphatics, and congestion and ventral consolidation of the lungs. Petechial hemorrhages have been seen on the pleural surfaces, and patchy hemorrhages may be found in the lung parenchyma. The airway often contains white or blood–tinged foam, and edema fluid oozes from cut tissues. Swollen and congested lymph nodes (especially lymph nodes associated with the respiratory tract), pleural and pericardial fluid, and visceral edema have also been reported. Scattered petechiae and ecchymoses may be found in the stomach, intestines and perirenal tissues. Yellowing of the subcutaneous tissue was reported to be common in some reports. Endometrial edema and purplish discoloration of the serosa of the uterus was reported in one experimentally infected mare. Vasculitis is the predominant lesion on histopathology.
Other animals

Post mortem lesions reported in a naturally infected, asymptomatic dog included respiratory lesions (diffuse reddening of the lungs, frothy fluid in the trachea and bronchi), enlargement and reddening of respiratory-associated lymph nodes, reddening of the tonsils, an enlarged liver and spleen, and prominent white streaks at the corticomedullary junction of the kidney. Severe pulmonary edema, hydrothorax and edematous bronchial lymph nodes were seen in experimentally infected cats. Some experimentally infected pigs had areas of consolidation in the lungs, with or without petechiae or larger, demarcated hemorrhagic areas. Petechial hemorrhages were also reported in other organs of some pigs, including the kidneys, bronchial and submandibular lymph nodes. Lesions found in experimentally infected ferrets included subcutaneous edema, petechial hemorrhages throughout the skin, the pulmonary parenchyma and the abdomen, and enlarged and hemorrhagic lymph nodes.

Diagnostic Tests

Stringent precautions should be used when collecting and shipping any diagnostic samples from live or dead animals. Only those samples that can be collected safely should be taken. A description of the limited necropsy procedure used to collect diagnostic samples, as well as necropsy and sample collection recommendations, can be found on the Web sites maintained by some states in Australia (see Internet Resources).

Sampling a variety of sites increases the probability of detecting Hendra virus. A combination of blood and nasal, oral and rectal swabs for PCR and/or virus isolation, and serum for serology, can detect a high proportion of infections in live horses. Other samples that may be taken include urine (e.g., a urine soaked swab taken from the ground immediately after urination), conjunctival swabs and swabs of other orifices (vaginal, urethral). Similar swab samples have been recommended for dead horses, together with blood collected from the jugular vein, and sampling of the superficial submandibular lymph node. Additional tissue samples (e.g., lung, kidney, lymphoid tissues, brain) may be collected by people experienced in sampling for Hendra virus.

PCR on blood, secretions and excretions (swabs) or tissue samples is often used for rapid diagnosis. Virus isolation can also be attempted in live animals; however, Hendra virus is more likely to be recovered from the tissues after death. Because this virus is a biosafety level 4 (BSL4) pathogen, virus isolation can only be done in a limited number of laboratories. Vero cells are often employed, but a number of other cell lines or primary cultures can also be used. The isolated virus can be identified by methods such as immunostaining or virus neutralization. Electron or immunoelectron microscopy may also be helpful.

Molecular methods (e.g., PCR), comparative immunostaining or differential neutralization assays can distinguish the closely related Hendra and Nipah viruses. Viral antigens can also be detected directly in tissues by immunoperoxidase or immunofluorescence assays.

Serology can be helpful, but horses may not have detectable titers until 10 to 14 days after infection. ELISAs and serum neutralization tests are used most often; the latter is considered to be the gold standard serological assay. False positives are common in ELISAs, which are often used as an initial screening test. Indirect immunofluorescence and immunoblotting have also been described. Cross-reactions can occur between Hendra and Nipah viruses in serological assays including virus neutralization; however, these reactions can be distinguished with comparative neutralization tests. Currently, there is no commercially validated test that can distinguish whether antibodies have resulted from infection or vaccination, but an experimental assay is reported to be available in Australia.

There is limited experience with diagnosis in animals other than horses. One naturally infected dog seroconverted without any virological evidence of infection. In another dog, PCR detected viral nucleic acids in blood and tissues, but not oral swabs, and virus isolation was unsuccessful. This animal was weakly seropositive at the time of euthanasia.

Treatment

Other than supportive therapy, there is no treatment for Hendra virus infections in animals. The current Australian policy is to euthanize surviving horses due to uncertainties about virus persistence. Infected dogs have also been euthanized for the same reason.

Control

Disease reporting

A quick response helps reduce human and animal exposure to infected horses, and also decreases the risk of a wider outbreak. Veterinarians who encounter or suspect a Hendra virus infection should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal veterinary authorities should be informed immediately. As of 2015, Australia also requires immediate notification of any infections in domesticated animals, although the virus is endemic in bats.

Prevention

A Hendra virus vaccine is now available for horses in Australia. Exposure to flying foxes, their tissues and secretions should also be minimized. Horse paddocks should not contain food trees favored by flying foxes, or trees planted in configurations that encourage roosting, and horses should be kept away from areas where flying foxes roost or are feeding. Whenever possible, feed bins and water troughs should be covered. Moving horses into
stables or other enclosures designed to keep them away from flying foxes at night is expected to be helpful.

Horses that develop signs consistent with Hendra virus infection should be isolated; they should not be allowed to contact other domesticated animals, as well as other horses. Stringent infection control measures should be employed to avoid spreading the virus on fomites. Human exposure must also be minimized. In Australia, unvaccinated horses that may have been exposed are assessed and tested for the disease, and vaccination may be recommended. Authorities may also require that any companion animals (e.g., dogs and cats) exposed to an infected horse be isolated for a period. Quarantines and rigorous hygiene have been effective in containing past outbreaks. The low rate of horse-to-horse transmission also aids control.

Carcasses should also be isolated until Hendra virus infection can be ruled out. Necropsies should be avoided unless the operator can carry them out safely using recommended guidelines and PPE (see human Prevention section). Government authorities should be consulted for the most appropriate disposal method for carcasses; deep burial on the property is currently considered the option of choice, although other options such as burning may also be used.

Morbidity and Mortality

The prevalence and shedding of Hendra virus seems to wax and wane in flying fox populations, but what causes these fluctuations is not known. Pregnancy, the birthing period and/or lactation were associated with Hendra virus infections in some studies, but not others, and their influence is currently uncertain. Other factors, such as nutritional stress, could also be involved, while environmental conditions such as the temperature might influence virus survival and transmission to horses. While Hendra virus can be shed year-round (though not constantly) in flying fox populations, infections appear to be seasonal in horses. Equine cases have occurred in the cooler months from May to October in subtropical areas, with a peak in July, although they have been seen year-round in the northern tropics.

Hendra virus infections seem to be uncommon in horses. As of July 2015, 94 cases had been reported in this species. The first cases were recognized during outbreaks in Hendra, Australia (Queensland) in 1994, but infections were rarely reported during the following decade; infected horses were found once in 1999, and on two occasions in 2004. The absence of any seropositive horses in two surveys, which tested approximately 4000 horses, also suggested that infections were rare. Hendra virus infections appeared more regularly between 2006 and 2009, with two incidents reported each year, and unexpectedly high numbers of cases were reported in 2011 (18 incidents with 23 cases) and 2012-2013 (12 incidents between January 2012 and July 2013). The reason for the recent increase in cases is unclear, although increased testing and recognition might play some role. The case fatality rate in recognized cases has been high and can approach 90%.

Other than in horses, the only naturally occurring infections that have been recognized (as of December 2015) were in two dogs on farms that had infected horses. In one of these incidents, only one of the three dogs on the farm became infected. In spite of their susceptibility to experimental infections, testing of cats on infected farms has revealed no natural infections in this species. A survey conducted in the Brisbane area, where the initial cases were reported in horses, also found no serological evidence of henipavirus infections in 500 cats. Likewise, an early survey reported that none of 100 swine herds tested in Queensland, Australia had antibodies to Hendra virus. Experimental infections in cats and guinea pigs have been fatal, but no clinical signs have yet been reported in naturally or experimentally infected dogs, and ferrets became ill but did not die.

Infections in Humans

Incubation Period

The initial symptoms occurred 5 to 16 days after exposure in six of the seven human cases. One person became ill after 21 days; however, he had been treated prophylactically with antiviral drugs, and developed encephalitis immediately afterward. It is possible that the treatment masked any initial influenza-like signs in this case. One person developed recurrent, fatal encephalitis a year after apparent recovery from the initial illness.

Clinical Signs

Hendra virus infections have been reported in seven people. The syndromes have included influenza-like illness, multiorgan failure and progressive encephalitis. The two initial cases were characterized by a serious influenza-like disease with fever, myalgia, respiratory signs and vertigo. One person died with pneumonitis, multiorgan failure and arterial thrombosis; the other recovered over the next six weeks. In the third case, a mild meningoencephalitic illness (drowsiness, headache, vomiting, neck stiffness) was followed by a long asymptomatic period before fatal encephalitis developed a year later. The fourth person reported a self-limited influenza-like illness with a dry cough, sore throat, cervical lymphadenopathy, fatigue, body aches and a fever that lasted for approximately one week.

Two cases in 2008-2009 were characterized by a biphasic illness that began with influenza-like signs (fever, myalgia and headache), followed by apparent recovery, then by recurrent fever and signs of encephalitis after 5-12 days. In one case, the neurological signs were limited to ataxia, mild confusion, bilateral ptosis and dysarthria, and the person survived, although with persistent neurological defects. The other person developed progressive, fatal neurological signs, beginning with ptosis, ataxia and mild confusion and progressing to seizures and coma. Another
fatal case occurred in a person who had been treated prophylactically for 5 days with antiviral drugs after exposure. He developed encephalitis, with signs of ataxia, drowsiness and seizures, immediately after drug treatment, and died after 19 days.

**Diagnostic Tests**

Hendra virus infections in humans have been diagnosed similarly to cases in horses, i.e., by tests such as PCR, virus isolation, antigen detection and immunohistochemistry.

**Treatment**

Treatment of Hendra virus infections, to date, has mainly been supportive. Antiviral drugs have been administered to some patients, as well as prophylactically in people at high risk of exposure; however, no antivirals have yet been shown to be effective against this disease. The efficacy of passively administered immunotherapy (monoclonal antibodies against Hendra virus) is under investigation.

**Control**

**Disease reporting**

People who have been exposed to Hendra virus should seek medical advice. In Australia, the area health department should be contacted to report the case.

**Prevention**

Human infections have been reported after nursing or examining sick horses, or handling equine tissues at necropsy. Stringent precautions should be taken to prevent contact with blood, tissues, body fluids and excretions whenever Hendra virus is among the differential diagnoses. Personal protective equipment (PPE) recommendations are available from government sources in Australia (see Internet Resources). In general, the minimum recommendations during an investigation of a suspected case include impervious gloves, a particulate (P2 [N95] or higher) respirator, a face shield or safety eyewear to protect the eyes, splash-proof overalls (or cotton or disposable overalls with impervious or splash-proof apron) and impervious boots. [NB: splash-proof rather than impervious overalls are recommended in Australia, due to dangers from overheating in a hot climate] Excellent hygiene should be practiced at all times, and caution should be used to avoid generating aerosols or splashing material, both when examining the horse and during disinfection. Detailed recommendations for conducting investigations of suspected Hendra virus infections, as well as precautions to be used when the likelihood of Hendra virus is first revealed during an examination of the case, are available from authorities in Australia.

Because Hendra virus infections can look like other diseases and are often diagnosed retrospectively, good infection control precautions (standard precautions) should be used routinely with horses whenever there is a risk of contact with blood, body fluids, excretions, mucous membranes or breaks in the skin. Veterinarians in endemic areas should keep a dedicated Hendra virus field kit with appropriate PPE, disinfectants, waste disposal bags and other necessary items for use in unexpected cases. All human exposure should be minimized once the case is suspected, and any contamination should be washed off with soap and water. Investigations should be continued only if suitable precautions can be taken and PPE is available.

**Morbidity and Mortality**

Hendra virus infections have been reported in seven people, all of whom had close contact with infected horses during their illness or at necropsy. Only a percentage of those exposed to infected horses have become ill. Two people, a stablehand and the trainer, were infected during an outbreak in 1994; the stablehand recovered but the trainer died. In a separate episode, a farmer who had close contact with two sick horses (both during their illness and at necropsy) became infected and died of the illness a year later. In 2004, a veterinarian who conducted the necropsy on an infected horse became ill but recovered. Two assistants at the necropsy remained seronegative. The same year, eighteen people were exposed to another infected horse or to its tissues at necropsy, but none seroconverted. No human infections were associated with the horses that died of this disease in 1999, 2006 or 2007, but illness was reported in a veterinarian and an animal nurse during one of the two clusters in 2008. A veterinarian was also infected during an outbreak in 2009. Two of the latter cases were fatal. Although there have been a number of people exposed to equine cases since that time (e.g., more than 60 people exposed to equine cases in 2011), no additional human cases were reported between 2010 and 2015. There has been no evidence of seroconversion in people who are often in close contact with flying foxes.

**Internet Resources**

Australian Veterinary Association (AVA). Appropriate PPE for Hendra virus investigation (video)
http://www.ava.com.au

Centers for Disease Control and Prevention, United States
http://www.cdc.gov/vhf/hendra/

New South Wales Department of Primary Industries.
Hendra Virus (includes guidelines for veterinarians handling cases)

Queensland Department of Agriculture and Fisheries.
Hendra virus (includes guidelines for veterinarians handling cases)
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*Link defunct as of 2015