Rabies and Rabies-Related Lyssaviruses

Hydrophobia, *Lyssa*

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Importance

Rabies is a viral disease that affects the central nervous system (CNS) of mammals and has an extremely high case fatality rate. Once the clinical signs develop, there are very few survivors. Vaccines can protect pets, as well as people exposed to these animals, but the maintenance of rabies viruses in wildlife complicates control. In humans, rabies can be prevented by administering anti-rabies antibodies and a series of vaccinations, provided exposure is recognized before the symptoms appear. However, people in impoverished countries do not always have access to effective post-exposure prophylaxis. Due to this and other factors, such as inadequate levels of vaccination in dogs and cats, the annual incidence of human rabies is estimated to be 40,000 or more cases, worldwide. A few cases occur even in nations with good medical care, typically in people who did not realize they were exposed. Human vaccines are also available, and provide some protection to people who are regularly exposed to the virus, but do not entirely eliminate the need for post-exposure prophylaxis.

Other lyssaviruses, closely related to rabies virus, circulate among bats in Europe, Asia, Australia and Africa. These viruses can cause an illness identical to rabies in people and domesticated animals. Rabies vaccines and post-exposure prophylaxis are thought to be protective against some of these viruses, but not others. Rabies-related lyssaviruses can be found even in countries classified as free of rabies virus.

Etiology

Rabies is caused by the rabies virus, a neurotropic virus in the genus *Lyssavirus*, family Rhabdoviridae. There are many variants (or strains) of this virus, with each variant maintained in a particular reservoir host. Although any variant can readily cause rabies in other species, it usually dies out during serial passage in species to which it is not adapted. The reservoir host is sometimes used as an adjective to describe a variant's origin. For example, if a virus from a skunk caused rabies in a dog, it would be described as skunk rabies in a dog, whereas a virus maintained in dog populations would be called canine rabies. Occasionally, a virus adapted to one species becomes established in another. In North America, canine rabies variants have become established in some species, such as foxes, skunks and mongooses, while bat rabies variants have adapted to transmission in raccoons and skunks. Similar host switching has been reported in other regions.

Closely related lyssaviruses, which are known as rabies-related lyssaviruses or nonrabies lyssaviruses, can cause a neurological disease identical to rabies. Viruses known to be pathogenic in humans or domesticated animals include Lagos bat virus, Duvenhage virus, European bat lyssavirus (EBLV) 1, EBLV 2, Australian bat lyssavirus (ABLV), Mokola virus and Irkut virus. All of these viruses, except Mokola virus, are thought to be maintained in bat populations. The reservoir host for Mokola virus, which has been found in wild rodents and shrews, is still uncertain. Some rabies-related lyssaviruses have (to date) been described only in bats, but can probably affect other mammals. These viruses include Shimoni bat virus, Aravan virus, Khujand virus, Bokeloh virus and West Caucasian bat virus. Ikoma virus is a newly described virus that was detected in the brain of an African civet (*Civettictis civetta*) with neurological signs. Several of these viruses were found in the last few years, and other rabies-related lyssaviruses will probably be discovered in the future.

Rabies and the rabies-related lyssaviruses have been classified into 2 or more phylogroups, based on their genetic relatedness. Viruses that are more closely related to rabies virus can be neutralized, at least to some extent, by antibodies to rabies virus. Phylogroup I contains the rabies virus, Duvenhage virus, EBLV 1, EBLV 2, Australian bat lyssavirus, Irkut virus, Aravan virus and Khujand virus. Bokeloh virus also appears to belong to this group. Phylogroup II consists of Lagos bat virus, Mokola virus and probably also Shimoni bat virus. West Caucasian bat virus has been provisionally placed in a new group, phylogroup III. Ikoma virus seems to be related to West Caucasian bat virus, although a full analysis is not yet available.

Unless otherwise specified, the information in this outline refers to the classical rabies virus.

Geographic Distribution

With some exceptions (particularly islands), the rabies virus is found worldwide. Some countries including the United Kingdom, Ireland, Sweden, Norway, Iceland, Japan, Australia, New Zealand, Singapore, most of Malaysia, Papua New Guinea, the Pacific Islands and some islands in Indonesia have been free of the classical rabies virus for many years. According to the World Health Organization (WHO), a country is considered to be free of rabies if there have been no indigenously acquired cases in humans or animals during the previous 2 years, in the presence of adequate surveillance and import regulations. Using this definition, several additional countries are considered to be rabies-free. In some cases, these nations have conducted rabies vaccination programs in wildlife, but are susceptible to the reintroduction of the virus from neighboring countries. Official lists should be consulted for the current list of rabies-free countries and areas, as it may change.

Rabies related lyssaviruses have been found only in the Eastern Hemisphere. There is limited information on the distribution of individual viruses within this area. EBLV 1, EBLV 2 and Bokeloh virus occur in Europe, Irkut virus and West Caucasian bat virus were detected in Russia, and Aravan virus and Khujand virus were found in Asia. Antibodies to West Caucasian bat virus have also been found in Africa, suggesting that it or a related virus might circulate there. Viruses that have been reported only from Africa include Duvenhage virus, Lagos bat virus, Mokola virus, Shimoni bat virus and Ikoma virus. Australian bat lyssavirus seems to be limited to Australia, but neutralizing antibodies to this or a related virus were detected among bats in the Philippines. Rabies-related lyssaviruses have not been found in the Americas, where the classical rabies virus is common among bats. The presence of a rabies-related lyssavirus does not prevent a nation from being listed as rabies-free. For example, these viruses have been isolated from bats and people in the United Kingdom and Australia, which are both considered to be free of rabies.

Transmission

The rabies virus is readily transmitted between mammals, whether they belong to the same or different species. This virus is usually spread in the saliva, when an infected animal bites another. Less often, an animal or person is infected by contact with infectious saliva or neurological tissues, through mucous membranes or breaks in the skin. The rabies virus is not transmitted through intact skin.

There are rare reports of transmission by other routes. A few cases have been reported after organ transplants, particularly corneas but also pancreas, kidneys, lung, liver and other tissues. Aerosol transmission has been documented in special circumstances, such as in laboratories and a bat cave with an unusually high density of aerosolized, viable virus particles. Rabies viruses have been transmitted by ingestion in experimentally infected animals, and there is anecdotal evidence of transmission in milk to a lamb and a human infant from their mothers. (More conventional routes could not be ruled out in the latter case.) Some authors have speculated that ingestion might play a role in rabies transmission among wild animals. In one epizootic among kudu, the virus may have spread between animals when they fed on thorn trees. There is no evidence that people have ever been infected by eating rabies virus (with the possible exception of the case described in the infant). As a precaution, however, post-exposure prophylaxis may be administered to people exposed by this route. This was the case in 2 incidents investigated by the U.S. Centers for Disease Control and Prevention (CDC), when people inadvertently drank unpasteurized milk from rabid cows. Although pasteurized milk and cooked meat are not expected to contain live virus (the rabies virus is inactivated by heat), ingesting any products from rabid animals is not recommended.

The dissemination of the rabies virus within the body

Immediately after infection, the rabies virus enters an eclipse phase during which it is not easily detected. During this phase, it replicates in non-nervous tissue such as muscle. It does not usually stimulate an immune response at this time, but it is susceptible to neutralization if antibodies are present. After several days or months, the virus enters the peripheral nerves and is transported to the central nervous system by retrograde flow in the axons. After dissemination within the CNS, where clinical signs develop as the neurons are infected, the virus is distributed to highly innervated tissues via the peripheral nerves. Most of the virus is found in nervous tissue, salivary glands, saliva and cerebrospinal fluid (CSF), which should all be handled with extreme caution.

Some virus has also been detected in other tissues and organs, including the lung, adrenal gland, kidney, bladder, heart, ovary, testis, prostate, pancreas, intestinal tract, cornea, germinal cells of hair follicles in the skin, sebaceous glands, tongue papillae and the brown fat of bats. The rabies virus is contained within the neurons, and handling most body fluids or intact organs is thought to be low risk. However, a puncture could theoretically pierce a neuron. Health care personnel are given post-exposure prophylaxis if they receive a needlestick or other puncture wound while caring for a rabies patient. Organ transplants also pose a risk, if the rabies infection is not recognized in the donor. Blood, urine and feces are not thought to be infectious; however, a few studies have suggested that viremia might be possible in some species. One study in mice, which used a polymerase chain reaction (PCR) assay to detect the virus, found viral RNA when the mice were ill, but not during the asymptomatic stage when virus was migrating to the CNS. It should be noted that the presence of RNA does not prove that infectious virus is present.

Epidemiological cycles

Rabies is maintained in two epidemiological cycles, one urban and one sylvatic. In the urban rabies cycle, dogs are the main reservoir host. This cycle predominates in areas where the proportion of unvaccinated and semi-owned or stray dogs is high. It has been virtually eliminated in North America and Europe; although sporadic cases occur in dogs infected by wild animals, the urban cycle is not perpetuated in the canine population.

The sylvatic (or wildlife) cycle is the predominant cycle in Europe and North America. It is also present simultaneously with the urban cycle in some parts of the world. The epidemiology of this cycle is complex; factors affecting it include the virus strain, the behavior of the host species, ecology and environmental factors. In any ecosystem, often one and occasionally up to 3 wildlife species are responsible for perpetuating a particular rabies variant. The disease pattern in wildlife can either be relatively stable, or occur as a slow moving epidemic. Examples of moving epidemics include a fox rabies epidemic that traveled slowly west in Europe, and a raccoon rabies epidemic that moved north along the east coast of the U.S. and into Canada.

Rabies-related Lyssaviruses

There is little information on the transmission of rabies-related lyssaviruses, although it is probably similar to rabies. Infections with these viruses have been reported after bites, scratches or close contact with bats. Bats inoculated with Eurasian bat lyssaviruses shed virus in saliva shortly before clinical signs developed. In one experiment, there was no evidence for transmission to uninoculated bats kept in the same cage.

Disinfection

The rabies virus can be inactivated by sodium hypochlorite, 45-75% ethanol, iodine preparations, quaternary ammonium compounds, formaldehyde, phenol, ether, trypsin, β-propiolactone, and some other detergents. It is also inactivated by a very low pH (below 3) or very high pH (greater than 11). This virus is susceptible to ultraviolet radiation. It is rapidly inactivated by sunlight and drying, and (in dried blood and secretions) it does not survive for long periods in the environment.

Infections in Humans

Incubation Period

In humans, the incubation period can be a few days to several years. Most cases become apparent after 1 to 3 months. In one study, approximately 4-10% of cases had an incubation period of 6 months or more.

Clinical Signs

Nonspecific prodromal signs may be seen during the early stage of rabies. They can include malaise, fever or headache, as well as discomfort, pain, pruritus or other sensory alterations at the site of virus entry. After several days, anxiety, confusion and agitation may appear, and progress to insomnia, abnormal behavior, hypersensitivity to light and sound, delirium, hallucinations, slight or partial paralysis, hypersalivation, difficulty swallowing, pharyngeal spasms upon exposure to liquids, convulsions and other neurological signs. Either an encephalitic (furious) form with hyperexcitability, autonomic dysfunction and hydrophobia, or a paralytic (dumb) form characterized by generalized paralysis, may predominate. Death usually occurs within 2 to 10 days.

Survival is extremely rare in clinical cases, and some survivors have been left with severe neurological deficits. However, there are also a few documented cases where patients with relatively mild neurological signs recovered well.

Rabies-related Lyssaviruses

Only a few human infections with rabies-related lyssaviruses have been reported. These patients developed neurological signs, similar to rabies, and nearly all cases were fatal. One child thought to have been infected with Mokola virus recovered; however, there is some question whether this child was actually infected with the virus. One preliminary study suggested that the pathology caused by these viruses might differ somewhat from rabies, with prominent inflammation and cell death (which is not seen with rabies virus) in the CNS.

Communicability

Human saliva contains the rabies virus, and transmission between people is theoretically possible, but unproven. Activities that could pose a risk for exposure include bites, kisses or other direct contact between saliva and mucous membranes or broken skin, sexual activity, and sharing eating or drinking utensils or cigarettes. It is not known how long humans can shed the virus before becoming symptomatic; the CDC recommends post-exposure prophylaxis for anyone who had at-risk contact with a person during the 14 days before the onset of clinical signs.

Iatrogenic transmission is also possible. There are several cases where rabies virus was transmitted to the recipient of a corneal transplant or transplanted internal organ. Needles or other sharp objects might also transmit the virus if they pass through human tissues, because there is a possibility they may have pierced nervous tissue. Feces, blood, urine and other body fluids are not thought to contain infectious virus.

Diagnostic Tests

Antemortem diagnosis is sometimes possible in human patients, using virus isolation, methods to detect rabies virus antigens or nucleic acids, and serology. RT-PCR or immunofluorescence may detect viral nucleic acids or antigens in saliva, or in skin biopsies taken from the nape of

the neck. In skin, the virus occurs in the cutaneous nerves at the base of the hair follicles. Rabies virus is sometimes found in corneal impressions or eye wash fluid, and RT-PCR may occasionally detect nucleic acids in CSF or urine. The virus can sometimes be isolated from the saliva, conjunctival secretions/tears, corneal impressions, skin biopsies or (less often) CSF in living patients. Mouse neuroblastoma (MNA) cells and other cell lines are usually employed. Animal inoculation into weanling mice was used extensively in the past; however, the World Health Organization recommends that this method be replaced by the rapid tissue culture infection test (RTCIT), whenever possible. More than one test is usually necessary for an antemortem diagnosis, as rabies virus is not invariably present in any tissue other than the CNS. Rabies is usually undetectable during the incubation period. Infections can also be difficult to diagnose when the clinical signs first appear.

Serological tests include indirect immunofluorescence, virus neutralization and enzyme-linked immunosorbent assays (ELISAs), and can be performed on serum or CSF. These assays (using serum) are often employed for purposes other than diagnosis, such as to assess specific antibody titers after vaccination. In people who are ill, the detection of antibodies in CSF is definitive, and indicates that the virus is replicating in the CNS. Circulating neutralizing antibodies do not usually appear until late, and infected people may still be seronegative when they die.

In patients who have died, immunofluorescence is usually used to detect rabies antigens in the brain. Other techniques such as immunohistochemistry, ELISA tests for antigens, virus isolation from brain samples, or RT-PCR may also be employed.

RT-PCR and tests based on monoclonal antibodies can identify rabies virus variants for epidemiological studies. These tests are usually done at reference laboratories.

Rabies-related Lyssaviruses

Infections with rabies-related lyssaviruses are easily misdiagnosed as rabies. The immunofluorescence test used for postmortem rabies diagnosis can detect these viruses, but does not recognize them as different from rabies virus. The specific virus can, however, be identified with tests based on monoclonal antibodies, or by PCR.

Treatment

Post-exposure prophylaxis consists of immediate wound cleansing, followed by the administration of human rabies immunoglobulin and several doses of human rabies vaccine. Fewer vaccine doses and no rabies immunoglobulin are given if the person was previously vaccinated. In unvaccinated patients, the recommended number of vaccine doses can vary with the availability of high quality biologicals and the performance of initial wound care. It is also influenced by whether the patient is immunocompetent or immunosuppressed. Post-exposure prophylaxis is highly effective if it is begun soon after exposure.

There is no single, recommended treatment once rabies symptoms develop. The ideal treatment is unknown, and both aggressive treatment and supportive therapy have a very high risk of failure. Experimental therapies including vaccines, antiviral drugs such as ribavirin, interferon-alpha, passively administered anti-rabies virus antibodies (human immunoglobulin or monoclonal antibodies), ketamine and/or the induction of a therapeutic coma have been tried in the past, but were usually ineffective. Some of these treatments, such as therapeutic coma, are controversial. One young patient who recovered well was treated with ribavirin, amantadine and supportive care including therapeutic coma (the "Milwaukee protocol"); however, the same treatment protocol has been unsuccessful in a number of other patients. Two young patients recently recovered with only supportive therapy. Currently, the CDC does not advocate either supportive therapy or aggressive treatment, and instead states that either may be offered.

If treatment is successful in sustaining life, the patient may be left with permanent, and possibly severe, neurological deficits. However, complete recovery or only mild deficits are also possible. Based on several recent cases, some authors have speculated that the best chance of successful treatment might be in young, healthy patients who have only mild neurological signs at presentation. The type/origin of the virus (e.g., bat rabies or canine rabies, or a less virulent strain) might also influence the outcome.

Prevention

Domesticated dogs, cats and ferrets should be vaccinated to prevent them from becoming infected and transmitting rabies to humans. Other domesticated animals may also be vaccinated, depending on the situation and risk of exposure. Stray animals should be controlled. Dogs, in particular, act as reservoirs for the canine rabies variant. Wild animals should not be handled or fed; wildlife behaving abnormally should especially be avoided. Bats should be kept out of houses and public buildings. In some areas, oral vaccination (via food bait) is used to reduce the incidence of rabies in wildlife reservoir hosts.

Veterinarians and animal control officers should handle potentially rabid animals with extreme caution. In addition to the risk of contracting rabies, these animals can be very unpredictable and can attack without warning. Protective clothing such as thick rubber gloves, eye goggles and a plastic or rubber apron should be worn when doing autopsies, or in other circumstances when exposure to infectious tissues could occur. Sick animals, including rabbits and rodents, should not be sent home if they have been exposed to potentially rabid wildlife, even if the clinical signs do not immediately suggest rabies.

Bites, needlestick injuries, and other human exposures to rabies virus should be reported immediately so that they may be evaluated, and any necessary post-exposure

prophylaxis can begin promptly. Non-bite exposures, defined as the contamination of mucous membranes or broken skin with saliva, nervous tissue, or other potentially infectious material, are evaluated for prophylaxis on a case-by-case basis.

To protect people from animals that may in the early stage of rabies, asymptomatic dogs, cats or ferrets that have bitten humans are observed for 10 days. If the animal develops signs of rabies during this time, it is euthanized and tested. It is not known whether the rabies status of lagomorphs and rodents can be determined by observation during a 10-day confinement. Until research establishes the viral shedding period in these species, human bites and scratches are evaluated individually for post-exposure prophylaxis. Factors that are considered include the animal's species, the circumstances of the bite and the epidemiology of rabies in the area, as well as the biting animal's history, current health status and potential for exposure to rabies. Similar considerations also apply when the companion animal belongs to other species in which the disease is incompletely understood.

Inactivated human vaccines are available for at risk veterinary staff, other animal handlers, wildlife officers, laboratory workers and others at high risk of exposure. International travelers may be vaccinated, depending on their destination and other risk factors. People in high risk occupations should have their antibody titers monitored periodically, with revaccination as needed. The recommended monitoring interval varies with the type and frequency of exposure. Vaccination does not eliminate the need for post-exposure prophylaxis; however, fewer doses of vaccine are needed, and rabies immunoglobulin is not required. It may also provide some protection if the person is unaware of the exposure or post-exposure prophylaxis is delayed.

Rabies-related Lyssaviruses

All currently licensed rabies vaccines are based on the classical rabies virus, and do not contain antigens from other lyssaviruses. Nevertheless, limited, preliminary studies in animals suggest that these vaccines may provide some protection against other phylogroup I viruses. Within this group, the amount of protection may vary with the specific virus. These studies also suggest that there is little or no protection against viruses in phylogroup II (Mokola virus, Shimoni bat virus and Lagos bat virus) or West Caucasian bat virus. In Europe, where phylogroup I viruses occur in bats, vaccination is recommended for people who regularly handle these animals. Precautions should also be taken to avoid bites and scratches. The use of protective gloves is one recommended measure. If an injury occurs, the wound should be cleansed and brought to the attention of a physician. Some sources recommend rabies booster vaccination/ post-exposure prophylaxis if the bat is not available for testing.

Morbidity and Mortality

The risk of developing rabies varies with factors such as a person's occupation, recreational activities and geographic location. People in some locations are at high risk from canine rabies, while exposure to wildlife is a more important factor in others. Rabies is a very common disease in some parts of the developing world. Worldwide, 10 million people are estimated to receive post-exposure prophylaxis each year, and 40,000 or more to die of this illness. Most of these cases occur in Africa and Asia, and over 90% are caused by rabid dogs. In contrast, human rabies is rare in countries where canine rabies has been controlled or eliminated, and effective post-exposure prophylaxis (with high quality reagents) is available. In the U.S., only 0-3 cases of rabies are usually reported in people, each year. In developed countries, rabies typically occurs in people who did not realize they were exposed, or for some other reason, did not seek medical treatment.

Without post-exposure prophylaxis, an estimated 20% of humans bitten by rabid dogs develop rabies. Factors that may affect the outcome of exposure include the virus variant or strain, dose, route of inoculation, and location of exposure, as well as host factors such as age and pre-existing immunity. In some cases, the virus may not be present in saliva at the time of the bite. Once the symptoms appear, rabies is almost always fatal, regardless of treatment. There are currently less than a dozen well-documented cases of survival, and only a few of these patients made a good recovery.

Until recently, all rabies survivors were people who received vaccine before the onset of symptoms (and it is also possible that some of these patients had post-vaccinal encephalomyelitis rather than rabies). Most were left with severe neurological complications. Since 2004, there have been at least 3 reports of young patients who survived with few or no residual neurological signs. Two of these patients were treated in the U.S., and one in India. All three had neutralizing antibodies to rabies virus at diagnosis, although none had been vaccinated. They also had relatively mild neurological signs when they were seen by a physician. One patient was treated aggressively with antiviral drugs and the induction of a therapeutic coma, but two others received only supportive therapy. One of these patients appeared to have been infected 2 years earlier.

These cases have renewed interest in determining whether subclinical infections might be possible in humans. In a recent study, neutralizing antibodies to rabies virus were found in 11% of the population, in a remote area of the Peruvian Amazon where infected vampire bats are common. None of the seropositive individuals reported symptoms consistent with rabies. A few previous studies found antibodies to rabies virus in 7-29% of study groups such as hunters, although most people had only low

antibody titers. Researchers still do not know whether seropositive individuals were exposed to inactivated or attenuated viruses, cleared a small viral dose that was insufficient to establish an infection, or eliminated the infection before it resulted in serious clinical signs. It is also possible that seropositive people were exposed to rabies-related lyssaviruses; however, this is unlikely as several studies were conducted in the Americas where these viruses are not known.

Rabies-related Lyssaviruses

There are only a few documented infections with rabies-related lyssaviruses. However, these infections might be underdiagnosed, as they can easily be mistaken for rabies. Some of the viruses also occur in areas where diagnostic capabilities and surveillance are limited. Viruses known to have caused illness in people include Duvenhage virus (3 cases), EBLV 1, EBLV 2 (2 cases), Australian bat lyssavirus (2 cases), Mokola virus (2 cases) and Irkut virus (1 case). All but one case (in a child who might have been infected with Mokola virus) were fatal. Recently, another child did not become ill after receiving a bite from an Ikoma virus-infected civet with neurological signs. It is uncertain whether the civet was shedding virus at the time of the bite. The child received wound care and post-exposure rabies vaccination, but its efficacy against this virus is not known.

Infections in Animals

Species Affected

All mammals are susceptible to rabies, but only a limited number of species also act as reservoir hosts. They include members of the Canidae (dogs, jackals, coyotes, wolves, foxes and raccoon dogs), Mustelidae (e.g., skunks), Viverridae (e.g., mongooses), and Procyonidae (raccoons), as well as members of the order Chiroptera (bats). Cat-adapted rabies variants have not been seen, although cats are often infected with rabies viruses from other hosts, and they can readily transmit the virus.

The most significant reservoir hosts vary with the geographic region. In North America, maintenance hosts for rabies virus include bats, striped skunks (*Mephitis mephitis*), raccoons (*Procyon lotor*) and various species of foxes. A coyote variant in Texas was eliminated by vaccination. Red foxes (*Vulpes vulpes*) and raccoon dogs (*Nyctereutes procyonoides*) are important hosts in Europe, and wolves can maintain the virus in parts of northern Europe. The canine rabies variant is well controlled in the U.S., Canada and Europe, and it may either no longer be circulating, or circulate only at very low levels. However, this virus has apparently become established in some wildlife populations and it could be re-established in dogs from these reservoirs.

Dogs are still the most important hosts in some parts of Africa, Asia, the Middle East and Latin America, although canine vaccination programs have controlled this variant in some locations. Bats maintain some rabies variants in Latin America, and vampire bats (*Desmodus rotundus*) are particularly important hosts in regions such as the Peruvian Amazon. Coyotes, skunks and foxes are also reported to be reservoir hosts in Latin America.. In the Middle East, red foxes and golden jackals (*Canis aureus*) are common hosts for rabies virus. Red and arctic foxes, raccoon dogs, mongooses and jackals may act as reservoir hosts in parts of Asia. Mongooses are also important in the Caribbean. In Africa, there is evidence that the virus might be maintained in jackals, foxes, mongooses, genets and other species.

Rabies-related Lyssaviruses

With the possible exception of Mokola virus, rabies-related lyssaviruses seem to be maintained in insectivorous bats and fruit bats. They also cause illness in these animals. Mokola virus has been detected in shrews and wild rodents, but not bats, and its reservoir host is still uncertain. The reservoir host for Ikoma virus, which was found recently in an African civet with neurological signs, is also unknown.

The susceptibility of other mammalian species is incompletely understood. Like rabies virus, rabies-related lyssaviruses might be able to infect all mammals. As of 2012, fatal neurological disease has been reported in cats, dogs and a water mongoose (*Atilax paludinosis*) infected with Lagos bat virus; cats and dogs infected with Mokola virus; cats, sheep and a stone marten infected with EBLV 1; and an African civet infected with Ikoma virus. Experimental infections with EBLV-1 were established in mice, sheep, foxes, ferrets, dogs and cats. It is quite likely that domesticated animals can also be affected by other lyssaviruses, such as Duvenhage virus, which has caused fatal illness in people.

Incubation Period

The incubation period varies with the amount of virus transmitted, virus strain, site of inoculation (bites closer to the head have a shorter incubation period), pre-existing host immunity and nature of the wound. In dogs, cats and ferrets, the incubation period is usually less than 6 months; most cases in dogs and cats become apparent between 2 weeks and 3 months. In cattle, the vampire bat variant is reported to have an incubation period of 25 days to more than 5 months. The incubation period is also usually less than 6 months in bats, although some individuals can remain asymptomatic for much longer.

Clinical Signs

The initial clinical signs are often nonspecific and may include fearfulness, restlessness, anorexia or an increased appetite, vomiting, diarrhea, a slight fever, dilation of the pupils, hyperreactivity to stimuli and excessive salivation. The first sign of post-vaccinal rabies is usually lameness in the vaccinated leg. Animals often have behavioral and temperament changes, and may become either unusually aggressive or uncharacteristically affectionate. Pigs

frequently have a very violent excitation phase at the onset of disease. After 2 to 5 days, these signs may be followed by a stage during which either the paralytic or the furious form of rabies predominates. Survival is extremely rare in either form of the illness.

The paralytic ("dumb") form of rabies is characterized by progressive paralysis. In this form, the throat and masseter muscles become paralyzed; the animal may be unable to swallow, and it can salivate profusely. Laryngeal paralysis can cause a change in vocalizations, including an abnormal bellow in cattle or a hoarse howling in dogs. There may also be facial paralysis or the lower jaw may drop. Ruminants may separate from the herd and can become somnolent or depressed. Rumination may stop. Ataxia, incoordination and ascending spinal paresis or paralysis are also seen. The paralytic form of rabies may be preceded by a brief excitatory phase, or none at all. Biting is uncommon. Death usually occurs within 2 to 6 days, as the result of respiratory failure.

The furious form of rabies is associated with infection of the limbic system, and is the more common form in cats. Large animals with this form, such as horses, are extremely dangerous due to their size. Furious rabies is characterized by restlessness, wandering, howling, polypnea, drooling and attacks on other animals, people or inanimate objects. Affected animals often swallow foreign objects such as sticks, stones, straw or feces. Wild animals frequently lose their fear of humans, and may attack humans or animal species they would normally avoid (e.g., porcupines). Nocturnal animals may be visible during the day. In cattle, unusual alertness can also be a sign of this form. Some animals have convulsions, especially during the terminal stages, and death sometimes occurs during a seizure. In most cases, however, the illness eventually progresses to incoordination and ascending paralysis. Animals with furious rabies usually die 4 to 8 days after the onset of clinical signs.

The signs of rabies can be highly variable, and many cases do not fit neatly into either the classic furious or paralytic presentation. The most reliable diagnostic signs are behavioral changes and unexplained paralysis, but rabies should be a consideration in all cases of unexplained neurological disease. For example, there have been cases in cats where no behavioral changes were noticed, and the illness appeared only as ataxia or posterior weakness, followed by ascending paralysis. Horses and mules are often in distress and extremely agitated, which may be interpreted as colic. Diagnosis can be particularly difficult in rabbits and rodents unless there is a history of exposure to a potentially rabid animal, such as a raccoon. Some infected rabbits developed obvious neurological signs, often of the paralytic form, but others had signs that were not initially suggestive of rabies, or experienced only nonspecific illness before death. In one report, sudden death was the only sign in many infected squirrels.

Rabies-related Lyssaviruses

Information about rabies-related lyssaviruses is currently limited to a handful of case reports and a few reports of experimental inoculation. In case reports, these viruses caused fatal neurological disease in various wild and domesticated animals.

Experimentally inoculated animals included mice, sheep, foxes, ferrets, dogs, cats and bats. Various inoculation routes, including intracerebral, intravenous and intramuscular injection, were used. Some animals developed severe neurological signs and died, while others were asymptomatic or had milder clinical signs and survived. Some mild cases might have resulted from using less virulent viruses (e.g., less pathogenic strains, or attenuated viruses propagated in the laboratory). For example, early studies suggested that phylogroup II viruses were less virulent than phylogroup I viruses; however, this is no longer thought to be true. Pre-existing immunity might also have contributed to survival in wild-caught bats.

The occurrence of healthy carriers among bats is controversial. There is one report that apparently healthy bats shed EBLV-1.

Communicability

All species of animals can transmit rabies viruses, but the efficiency of transmission varies with the host and the form of rabies. Animals with the furious form are more likely to spread rabies than animals with the paralytic form. Carnivores are also more efficient vectors, in general, than herbivores. Herbivore-to-herbivore transmission is uncommon. Vampire bats are often responsible for outbreaks among livestock in South America, but insectivorous bats can also transmit rabies.

Virus shedding is estimated to occur in 50-90% of infected animals. Depending on the species of animal and the viral strain, the amount of virus in the saliva varies from a trace to high titers. Shedding can begin before the onset of clinical signs. Cats have been reported to excrete virus for 1-5 days before the signs appear, cattle for 1-2 days, skunks for up to 14 days and bats for 2 weeks. Virus shedding in dogs is usually said to be limited to 1-5 days before the onset of clinical signs; however, in some experimental studies (using viruses of Mexican or Ethiopian origin), the virus was present in the saliva for up to 13 days before the dogs became ill.

The possibility that animals might carry lyssaviruses asymptomatically is controversial, and has not been unequivocally demonstrated. If it happens at all, it seems to be very rare. There are two reports of virus shedding without clinical signs in bats. Possible cases were also reported among dogs in Ethiopia and India, including one experimentally infected dog that recovered from clinical rabies and appeared to carry the virus in the saliva and tonsils, but not in the brain or other organs.

Post-Mortem Lesions

There are no characteristic gross lesions. The stomach may contain various abnormal objects, such as sticks and stones. The typical histological signs, found in the central nervous system, are multifocal, mild, polioencephalo-myelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells, and glial nodules. Negri bodies can be seen in some but not all cases.

Diagnostic Tests

In animals, rabies virus is usually identified by immunofluorescence in a brain sample taken at necropsy. The virus might also be found in other tissues such as the salivary gland, skin (tactile facial hair follicles) and corneal impression smears, but detection is less efficient. In the brain, immunofluorescence can identify 98-100% of cases caused by all genotypes of the rabies and rabies-related lyssaviruses. The usual assay does not, however, distinguish the different viruses. Immunofluorescence is most effective on fresh samples. Rabies can also be diagnosed with immunohistochemistry and ELISAs that detect antigens. RT-PCR can be useful, particularly when the sample is small (e.g., saliva) or when large numbers of samples must be tested in an outbreak or epidemiological survey. Histology to detect aggregates of viral material in neurons (Negri bodies) is nonspecific, and it is not recommended if more specific techniques are available.

A single negative test does not rule out infection; therefore, virus isolation in cell culture is often done concurrently. Mouse inoculation may also be used in some circumstances, but cell culture is preferred. Identification of rabies virus variants or other species of lyssaviruses is done in specialized laboratories using monoclonal antibodies, specific nucleic acid probes, or RT-PCR followed by DNA sequencing.

Serology is occasionally used to test seroconversion in domesticated animals before international travel, as well as during wildlife vaccination campaigns or in research. It is rarely useful for the diagnosis of clinical cases, as the host usually dies before developing antibodies. Serological tests include virus neutralization tests and ELISAs. The rabies virus and rabies-related lyssaviruses cross-react, but the assays do not detect antibodies to most other rhabdoviruses. Some cross-reactive epitopes have been reported in members of the *Ephemerovirus* genus (bovine ephemeral fever virus and closely related viruses).

Treatment

There is no treatment once the clinical signs appear. Post-exposure prophylaxis of animals is usually considered inadvisable because it may increase human exposure. These procedures have not been validated and are either prohibited or not recommended in the U.S. and many European countries. This is not the case in all parts of the world, and commercial vaccines are licensed for this purpose in some countries.

Prevention

In animals, rabies prevention is based on vaccination and the avoidance of contact with infected animals. Pets kept from roaming are less likely to encounter a rabid domesticated or wild animal, and also less likely to spread rabies if they become infected. Pet rabbits and rodents (which are not usually vaccinated) are safer if they are housed indoors. They should be watched closely if they are allowed outside to exercise. Rabbits kept outside should be in an elevated, double-walled hutch that does not have exposed wire mesh floors. As much as possible, domesticated animals should be kept away from wild animals, especially those that behave unusually. Bats caught by cats should be submitted for rabies testing. Six-month quarantines have been recommended for all wild-caught mammals added to collections. This is expected to identify most infected animals, though rare cases may become apparent after this time.

Rabies vaccines are available for dogs, cats, ferrets, cattle, sheep and horses. Both inactivated and modified live vaccines are effective, but rare cases of post-vaccinal rabies have been reported with the modified live vaccines in dogs and cats. Vaccines have not been validated in rabbits or rodents, although they might be used extralabel in petting zoos or other facilities where animals are in contact with the public. Vaccination programs in wildlife, using oral vaccines, protect domesticated animals as well as people. In countries with large stray dog populations, similar vaccines may be useful.

Rabies vaccines (which are all based on the classical rabies virus) seem to provide little or no protection from rabies-related lyssaviruses in phylogroup II (Mokola virus, Shimoni virus and Lagos bat virus) or those provisionally classified in phylogroup III (e.g., West Caucasian bat virus). Some pets that died from Lagos bat virus and Mokola virus infections had been vaccinated against rabies. In contrast, limited vaccination and challenge studies suggest that rabies vaccines may provide some degree of cross-protection against rabies-related lyssaviruses in phylogroup I. (e.g., European bat lyssaviruses). Within phylogroup I, the amount of protection may vary with the specific virus.

If an unvaccinated animal is exposed to rabies virus, authorities recommend that it be euthanized and tested. This prevents unnecessary prophylaxis in people who may have been exposed, and also reduces the risk that it will infect other people or animals. If the owner is unwilling to allow euthanasia, the animal may be placed in strict isolation for 6 months. In the U.S., dogs, cats and ferrets placed in such quarantines may be vaccinated either upon entry into isolation or up to 28 days before release. Livestock, rabbits and other animals are isolated but not necessarily vaccinated. If a vaccinated animal is exposed to rabies in

the U.S., it is revaccinated and confined under observation for 45 days. Animals with expired vaccinations are evaluated on a case-by-case basis. Asymptomatic dogs, cats or ferrets that have bitten humans (with no history of exposure to rabies) are currently observed for 10 days. If the animal develops signs of rabies during this time, it is euthanized and tested. Vaccination is not recommended during the 10-day observation period, as rare vaccine side effects could be confused with rabies.

Most countries have regulations to prevent the importation of rabies in animals. These regulations vary with the country and animal species, and may include quarantine or testing for vaccine-induced seroconversion. Some countries that formerly required a long quarantine period for pets will now allow vaccinated pets to enter with serological evidence of an adequate antibody titer.

Morbidity and Mortality

The incidence of rabies in animals varies with the region. Canine rabies was once very common in most countries, and it is still common in some parts of Africa, Asia, the Middle East and Latin America. In other areas, including all of the U.S., Canada and Europe, rabies has been controlled in dogs, or even eradicated. The reduction in canine rabies has been dramatic. In the U.S., approximately 5,000 cases occurred in dogs during 1946, but only 69 rabid dogs were reported in 2010. In countries where canine rabies has been controlled, wildlife reservoirs have become important in the epidemiology of this disease.. In 2010, wild animals accounted for more than 90% of the rabies cases reported in both the U.S. and Canada. In the U.S.: 37% of these cases were in raccoons, 24% occurred in skunks, 23% in bats and 9% in foxes.

In some countries such as the U.S., cats are now more likely to develop rabies than dogs, probably due to the lower vaccination rates in this species, combined with greater exposure to wildlife. Cases also occur in other species, including livestock. Rabies is reported infrequently in ferrets, and rarely documented in rabbits and rodents. In domesticated animals, rabies cases tend to be sporadic, but epizootics are possible. In South America, outbreaks occur among cattle bitten by vampire bats. Epizootics have also been reported among wildlife such as kudu (*Tragelaphus strepsiceros*) in Africa. Rabies can be a serious concern in some populations of rare or endangered species. In Africa, the Ethiopian wolf (*Canis simensis*) and African wild dogs (*Lycaon pictus*) are threatened by this virus.

All animals exposed to the rabies virus do not become ill. Factors that may affect the outcome of exposure include the virus variant, dose of virus, route and location of exposure, and host factors such as the species of animal, age and existing immunity to lyssaviruses. Although bats can die of rabies, antibodies to lyssaviruses are relatively common in this species. Worldwide, the seroprevalence rates in wild bat populations range from 5% 50%. Experiments also suggest that some bats inoculated with rabies survive, and can become immune to the virus. In one study, 36-40% of a group of bats died, each of the first two times they were inoculated with rabies virus; however, only one of the 16 surviving bats died when they were inoculated a third time. In contrast, neutralizing antibodies seem to be uncommon (e.g., 0–5%) among terrestrial carnivores such as foxes. Nevertheless, there is experimental evidence that some carnivores might not become succumb to the virus after exposure. In one study, 8 of 47 inoculated dogs survived, and were subsequently resistant to reinfection. Four of 10 dogs survived and became seropositive in another report. Antibodies have also been found in a few cats with no history of vaccination. Reports of animals surviving after the development of clinical signs are very rare, but do exist. In one well-documented case, an experimentally infected ferret (skunk origin virus) developed neurological signs and had evidence of infection in the CSF, but recovered with persistent hindlimb paralysis. There was no evidence of any residual virus at the time of euthanasia.

Rabies-related Lyssaviruses

Both the incidence of infections with rabies-related lyssaviruses and the case fatality rate are unknown. Although some of these viruses are common in bats, only a few clinical cases have been reported in domesticated animals. All of these cases were fatal. Experiments with intramuscularly inoculated dogs and cats suggested that cats might be more susceptible to EBLV-1 than dogs. While dogs survived and developed neutralizing antibodies, infections in cats were fatal.

Internet Resources

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/rabies/

Compendium of Animal Rabies Prevention and Control, 2011
http://www.cdc.gov/mmwr/pdf/rr/rr6006.pdf

International Veterinary Information Service (IVIS)
http://www.ivis.org

Public Health Agency of Canada. Pathogen Safety Data Sheets
http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

World Health Organization
http://www.who.int/mediacentre/factsheets/fs099/en/

World Organization for Animal Health (OIE)
http://www.oie.int/

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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*Link defunct as of 2012