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 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, illness 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.

Closely related lyssaviruses circulate among bats in the Eastern Hemisphere, and can cause an illness identical to rabies in people and domesticated animals. Rabies vaccines and post-exposure prophylaxis are thought to provide some protection against some of these viruses, but not others. Rabies-related lyssaviruses can be found even in countries classified as rabies-free.

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, each maintained in a particular reservoir host. The reservoir host may be reflected in the case description. For example, if a virus maintained in skunks caused rabies in a dog, it would be described as skunk rabies in a dog, rather than canine rabies.

Closely related lyssaviruses, which are known as rabies-related lyssaviruses or nonrabies lyssaviruses, can cause a neurological disease identical to rabies. Lagos bat virus, Duvenhage virus, European bat lyssavirus (EBLV) 1, EBLV 2, Australian bat lyssavirus (ABLV), Mokola virus and Irkut virus have caused clinical cases in humans or domesticated animals, and Ikoma virus was detected in the brain of an African civet (*Civettictis civetta*) with neurological signs. Shimoni bat virus, Aravan virus, Khujand virus, Bokeloh virus and West Caucasian bat virus have been found, to date, only in bats, but might be pathogenic in other species. Additional rabies-related lyssaviruses are likely to exist.

Rabies virus and the rabies-related lyssaviruses have been classified into two 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 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.

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 families Canidae (dogs, jackals, coyotes, wolves, foxes and raccoon dogs), Mustelidae (e.g., skunks), Viverridae (e.g., mongooses), and Procyonidae (raccoons), and the order Chiroptera (bats). Although cats can be affected by rabies, cat-adapted variants have not been seen. Each rabies variant is maintained in a particular host, and usually dies out during serial passage in species to which it is not adapted. However, any variant can cause rabies in other species. Occasionally, a virus adapted to one species becomes established in another.

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, such as some parts of Africa, Asia, the Middle East and Latin America. The urban rabies cycle has been virtually eliminated in the U.S., Canada and Europe; although sporadic cases occur in dogs infected by wild animals, the urban cycle is not

perpetuated in canine populations. However, the canine rabies variant is apparently established in some wildlife populations (e.g., foxes and skunks in North America) and it could be re-established in dogs from these reservoirs.

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. Some wildlife maintenance hosts include skunks and bats in the Americas, raccoons (*Procyon lotor*) in North America, raccoon dogs (*Nyctereutes procyonoides*) in Europe and Asia, and wolves in northern Europe. Various foxes are reservoir hosts in Europe, North America, the Middle East and Asia, and mongooses maintain rabies viruses in Asia and the Caribbean. Coyotes are reported to be reservoir hosts in Latin America, and jackals in the Middle East and Asia. Several species including jackals, foxes, mongooses and genets might maintain viruses in Africa.

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 is also unknown.

The susceptibility of other mammalian species to rabies-related lyssaviruses is incompletely understood. Like rabies virus, these viruses 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 likely that domesticated animals can also be affected by other lyssaviruses, such as Duvenhage virus, which has caused fatal illness in people.

Zoonotic potential

All rabies variants are thought to be zoonotic. Clinical cases have also been caused by Duvenhage virus, EBLV 1, EBLV 2, Australian bat lyssavirus, Mokola virus and Irkut virus. Humans are likely to be susceptible to other rabies-related lyssaviruses.

Geographic Distribution

With some exceptions (particularly islands), rabies virus is found worldwide. Some countries such as the United Kingdom, Ireland, Sweden, Norway, Iceland, Japan, Australia, New Zealand, Singapore, most of Malaysia, Papua New Guinea, the Pacific Islands and some Indonesian islands have been free of this 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 have been found in Asia. Antibodies to West Caucasian bat virus were also 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 found among bats in the Philippines. Rabies-related lyssaviruses have not been detected 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.

Transmission

Rabies virus has an unusual dissemination pattern in the body, which influences its transmission, diagnosis and prevention. Immediately after infection, the virus enters an eclipse phase during which it replicates in non-nervous tissue (e.g., muscle), and is not easily detected. 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 CNS. 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. The virus is concentrated in nervous tissue, salivary glands, saliva and cerebrospinal fluid (CSF), which should all be handled with extreme caution. Limited amounts of virus have been detected in a number of other tissues and organs. Because the virus is contained within neurons, handling most body fluids or intact organs is thought to be low risk. However, a few cases of rabies have been reported in organ transplant recipients. Corneas were often involved, but various internal organs have also transmitted rabies. Needles or

other sharp objects might transmit the virus if they pass through 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.

Rabies virus is usually spread between animals in the saliva, during a bite from an infected animal. Less often, an animal or person is infected by contact with infectious saliva or neurological tissues, through mucous membranes or breaks in the skin. This virus is not transmitted through intact skin. The efficiency of transmission varies with the behavior of the infected animal. 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.

Not all rabid animals will transmit the virus to animals they bite. Virus shedding is estimated to occur in 50-90% of infected animals, and the amount of virus in the saliva varies from a trace to high titers. It can be influenced by the species of animal and the viral strain. 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 to 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. In very rare cases, it has been suggested that bats or dogs might be able to carry lyssaviruses asymptomatically, but this is controversial, and has not been unequivocally demonstrated.

Human saliva contains 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 U.S. Centers for Disease Control and Prevention (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.

There are rare reports of transmission by other routes. Aerosol transmission has been documented under 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 (*Tragelaphus strepsiceros*), 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).

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

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 Animals

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 vocalization, 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 and stones. 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 the case reports, these viruses caused fatal neurological disease in various wild and domesticated animals. Various inoculation routes, including intracerebral, intravenous and intramuscular injection, were used in several species of experimentally infected animals. 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.

Post Mortem Lesions

There are no characteristic gross lesions. The stomach may contain unusual objects that were ingested. The typical histological signs, found in the CNS, are multifocal, mild, polioencephalomyelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells, and glial nodules. Aggregates of viral material in neurons (Negri bodies) can be seen in some but not all cases.

Diagnostic Tests

In animals, rabies virus is usually identified by detecting viral antigens 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. Immunofluorescence is the most commonly used assay, and is most effective on fresh samples. It can identify 98-100% of cases caused by all genotypes of the rabies and rabies-related lyssaviruses, using brain tissues. The usual immunofluorescence assay cannot, however, distinguish these viruses. Immunohistochemistry and enzyme-linked immunosorbent assays (ELISAs) can also be used to 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 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 (e.g., mouse neuroblastoma cells) 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 diagnosing clinical cases, as the host usually dies before developing antibodies. Serological tests include virus neutralization tests and ELISAs. 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, as described below for humans, is usually considered inadvisable because it may increase human exposure. Post-exposure prophylactic procedures for animals 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.

Control

Disease reporting

A quick response is important for minimizing exposure to a rabies case, even in endemic regions. Veterinarians who encounter or suspect rabies should follow their national and/or local guidelines for disease reporting. In the U.S., state authorities must be notified immediately.

Prevention

In animals, rabies prevention is based on vaccination and the avoidance of contact with infected animals (e.g., preventing pets from roaming, housing pet rabbits and rodents indoors). Rabbits kept outside should be in an elevated, double-walled hutch that does not have exposed wire mesh floors. 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.

Vaccination is recommended for dogs, cats and ferrets, to reduce human exposure as well as to protect the animal. Both inactivated and modified live vaccines are effective in dogs and cats, but rare cases of post-vaccinal rabies have been reported with modified live vaccines. Rabies vaccines are also available for livestock. 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 oral vaccines may be useful.

Rabies vaccines are all based on rabies virus, and seem to provide little or no protection from rabies-related lyssaviruses in phylogroup II or those provisionally classified in phylogroup III. Limited vaccination and challenge studies suggest that they may provide some cross-protection against rabies-related lyssaviruses in phylogroup I. Within phylogroup I, the amount of protection may vary with the specific virus.

The specific regulations for domesticated animals exposed to a rabid animal vary with the country, species of animal and vaccination status. If an unvaccinated animal is exposed to rabies virus in the U.S., 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. 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.

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.

Morbidity and Mortality

The incidence of rabies in domesticated animals varies with the region. Canine rabies was once very common worldwide, but it has been controlled, or even eradicated, in some countries. In some countries (e.g., 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. Rabies is reported infrequently in ferrets, and rarely documented in rabbits and rodents. Sylvatic and urban rabies cycles occur concurrently in some regions, while the sylvatic cycle predominates in others. For example, wild animals accounted for more than 90% of the animal rabies cases reported in the U.S. and Canada in 2010. Rabies can be a serious concern in some rare or endangered species. In Africa, the Ethiopian wolf (*Canis simensis*) and African wild dogs (*Lycaon pictus*) are threatened by this virus. Although cases of rabies tend to be sporadic, epizootics are possible. Outbreaks occur among cattle bitten by vampire bats (*Desmodus rotundus*) in South America. Epizootics have also been reported occasionally among wildlife, such as kudu in Africa.

All animals exposed to rabies virus do not become ill. Factors that may affect the outcome of exposure include the virus variant, presence in saliva at the time of the bite, dose of virus, route and location of exposure, and host factors such as the species of animal, age and existing immunity to lyssaviruses. Experiments in bats and dogs suggest that some animals can survive and become resistant to reinfection. 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

Although some rabies-related lyssaviruses are common in bats, only a few clinical cases have been reported in domesticated animals. All of these cases were fatal.

Infections in Humans

Incubation Period

In humans, the incubation period can be a few days to several years. Most cases become apparent after 1-3 months.

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 survivors are often left with severe neurological deficits. However, there are a few documented cases where patients with relatively mild neurological signs recovered well.

Rabies-related Lyssaviruses

Only a few infections with rabies-related lyssaviruses have been reported. These patients developed neurological signs, similar to rabies, and nearly all cases were fatal.

Diagnostic Tests

Antemortem diagnosis is sometimes possible in people with rabies symptoms. 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. Virus isolation is sometimes possible from the saliva, conjunctival secretions/tears, corneal impressions, skin biopsies or (less often) CSF in living patients. More than one test is usually necessary for an antemortem diagnosis, as the virus is not invariably present in any tissue other than the CNS. Detecting antibodies to rabies virus in CSF is definitive, and indicates that the virus is replicating in the CNS. Neutralizing antibodies do not usually appear in the blood until late, and infected people may still be seronegative when they die. Rabies is usually undetectable during the incubation period. After death, rabies virus can be detected in the brain, as in animals.

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, the performance of initial wound care, and whether the patient is immunocompetent or immuno-suppressed. 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. A number of experimental therapies (e.g., vaccines, antiviral agents, antibodies to rabies virus, ketamine and/or the induction of a therapeutic coma) have been tried in the past, but were usually ineffective. Some 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.

Control

Controlling rabies in domesticated and wild animals, mainly through vaccination, reduces the risk of exposure in humans. 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. Although pasteurized milk and cooked meat are not expected to contain infectious rabies virus, which is inactivated by heat, ingesting any product from a rabid animal is not recommended.

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 exposures 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 be in the early stage of rabies, asymptomatic dogs, cats or ferrets that have bitten humans are confined under observation for a short period (e.g., for 10 days in the U.S.). 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, but fewer treatments are needed. 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 vaccines are based on 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. In Europe, vaccination is recommended for people who regularly handle bats and may be exposed to lyssaviruses. Precautions should also be taken to avoid bites and scratches. 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. 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. 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 (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. 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 the other two received only supportive therapy. One of these patients appeared to have been infected 2 years earlier. The reasons for their good outcomes are uncertain, but potential factors include the patients' young age and good health, the mild neurological signs at presentation, or the type/origin of the virus (e.g., a less virulent strain). Based on limited serological evidence, especially in one South American population, it appears that subclinical infections might also be possible in humans. However, this remains to be proven.

Rabies-related Lyssaviruses

Infections with rabies-related lyssaviruses seem to be rare, but might be underdiagnosed, as they can easily be mistaken for rabies. Some of these viruses also occur in areas where diagnostic capabilities and surveillance are limited. Almost all symptomatic cases have been 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. Recently, another child did not become ill after receiving a bite from an Ikoma virus-infected civet with neurological signs. The child received wound care and post-exposure rabies

vaccination, but its efficacy against this virus is not known. It is uncertain whether the civet was shedding virus at the time of the bite.

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.html

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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