Rabies and Rabies-Related Lyssaviruses

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Importance

Rabies is a severe viral disease that affects the central nervous system (CNS) of mammals. Survival is very rare once the clinical signs develop, and only a few humans or animals have ever recovered without severe neurological deficits. Rabies viruses can be maintained in various wildlife hosts, complicating their control, as well as in dogs. While disease in humans and domestic animals in usually the primary concern, the illness can also be a serious issue in some wildlife, including rare or endangered species such as the Ethiopian wolf (*Canis simensis*) and African wild dog (*Lycaon pictus*). Vaccines can protect pets and livestock, as well as people exposed to these animals, and human illness can be prevented by administering 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, human rabies continues to be a significant problem in some parts of the world. A few cases occur even in nations with good medical care and widespread vaccination of pets, 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. Rabies vaccines and post-exposure prophylaxis can 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 virus is a neurotropic virus in the genus *Lyssavirus*, family Rhabdoviridae. Each viral variant is maintained in a particular reservoir host, and the name of this host is often part of 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 viruses, called rabies-related lyssaviruses or nonrabies lyssaviruses, are maintained in bats and can cause illnesses identical to rabies.

Rabies virus and related viruses have been classified into several phylogroups, based on their genetic relatedness. Phylogroup I contains rabies virus, Duvenhage virus, European bat lyssavirus (EBLV) 1, EBLV 2, Australian bat lyssavirus (ABLV) and Irkut virus, which are all known to affect humans and/or domestic animals; as well as some viruses, such as Bokeloh bat lyssavirus, Aravan virus, Gannoruwa bat lyssavirus, Khujand virus and Kotalahti bat lyssavirus, which have only been detected in bats, to date. Shimoni bat virus, Lagos bat virus and Mokola virus belong to phylogroup II, while West Caucasian bat virus, Ikoma virus and Lleida bat lyssavirus are classified in one or more additional phylogroups. Of the latter group of viruses, Lagos bat virus, Mokola virus and Ikoma virus have been reported from clinical cases in humans or animals other than bats. Additional rabies-related lyssaviruses (e.g., Matlo bat lyssavirus, Taiwan bat lyssavirus) have been proposed and there are probably viruses that have not yet been discovered.

Species Affected

All species of mammals can probably contract rabies, but only a limited number also act as reservoir hosts. Reservoir hosts are mostly members of the families Canidae (dogs, jackals, coyotes, wolves, foxes, raccoon dogs), Mustelidae (various skunks, ferret badgers), Viverridae (mongooses, genets), and Procyonidae (raccoons), and the order Chiroptera (bats). Some unusual reservoirs have been proposed for a few variants, including common/ white-tufted marmosets (*Callithrix jacchus*) in parts of Brazil, and greater kudu (*Tragelaphus strepsiceros*) in one region in Africa. Although cats can be affected by rabies, cat-adapted variants have not been seen.

Birds can be infected with rabies virus, based on experiments with orally or parenterally inoculated animals, as well as rare reports of naturally acquired infections. The latter are often anecdotal, and were mostly described in the older literature; however, a confirmed infection was recently described in a chicken that died after a brief illness, a few weeks after a dog bite. Clinical cases seem to be unusual, even in experimentally infected birds.

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Epidemiology of rabies

Rabies viruses are maintained in two types of cycles, urban and sylvatic. In the urban cycle, dogs act as the reservoir host for a rabies variant that circulates in canine populations. At one time, the urban cycle was found in much of the world; however, it is now usually seen only where vaccination rates in dogs are inadequate. The canine rabies variant can still be found in foxes and skunks in North America, and it could become re-established in dogs if vaccination programs were stopped.

Various wild mammals maintain rabies viruses in sylvatic cycles. The epidemiology of sylvatic rabies is complex but generally one to a few wildlife species perpetuate a particular variant in each area, either as reservoirs or important secondary hosts. The disease pattern in these animals can either be relatively stable, or occur as a slow-moving epidemic. Some important sylvatic maintenance hosts include raccoons (*Procyon lotor, P. cancrivorous*), foxes, coyotes, various skunks, bats and possibly common marmosets in the Americas; Indian mongooses (*Herpestes auropunctatus*) in the Caribbean; jackals, foxes, wolves, raccoon dogs (*Nyctereutes procyonoides*), Chinese ferret badgers (*Melogale moschata*) and mongooses in parts of Asia; and foxes in Europe. The wildlife situation is less clear in Africa, where canine rabies is still prevalent; however, several species including jackals, foxes, mongooses and genets are thought to maintain rabies viruses, greater kudu have been proposed as a possible reservoir for one variant, and other species such as hyenas might also play a role.

Rabies-related Lyssaviruses

Most rabies-related lyssaviruses are maintained in insectivorous bats and fruit bats. Mokola virus was found in shrews and wild rodents but not bats, and its reservoir host is uncertain. The reservoir host for Ikoma virus is unknown.

Clinical cases occur in some bats, and have also 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 (*Martes foina*) infected with EBLV 1; horses infected with Australian bat lyssavirus; and an African civet (*Civettictis civetta*) infected with Ikoma virus. Irkut virus RNA was found in the brain of a dead dog, though not definitively identified as the cause of death. Experimental infections confirmed rabies symptoms in mice, sheep, foxes, ferrets, dogs and cats infected with EBLV 1, and dogs and cats infected with Irkut virus. Like rabies virus, these and other rabies-related lyssaviruses can probably affect a wide variety of mammals, and possibly some birds.

Zoonotic potential

All variants of rabies virus 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 probably susceptible to other rabies-related lyssaviruses as well.

Geographic Distribution

With some limited exceptions, rabies viruses can be found worldwide. Most cases in humans and domestic animals occur in impoverished regions, especially in Africa and Asia, where the urban rabies cycle still exists. Sylvatic cycles can be found in much of the world, though a few countries have controlled wildlife rabies with oral vaccines. Rabies virus is entirely absent from only a few nations, typically islands, including the United Kingdom, Ireland, Japan, Australia and New Zealand. Taiwan was also thought to be rabies-free; however, expanded wildlife surveillance after 2012 found the virus in Chinese ferret badgers, which act as the reservoir, and other animals. The World Health Organization (WHO) considers a country 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, including some European nations, are considered to be rabies-free.

Bats in the Western Hemisphere are reservoir hosts for rabies virus; however, bats in the Eastern Hemisphere carry rabies related lyssaviruses instead. The latter viruses appear to circulate in most or all parts of the Eastern Hemisphere. There is limited information on the distribution of individual viruses, but EBLV 1, EBLV 2, Bokeloh virus, Lleida bat lyssavirus and Kotalahti bat lyssavirus have been found in Europe; Irkut virus and West Caucasian bat virus were detected in Russia; Irkut virus, Aravan virus, Gannoruwa bat lyssavirus and Khujand virus have been found in Asia; Duvenhage virus, Lagos bat virus, Mokola virus, Shimoni bat virus, Ikoma virus and either West Caucasian bat virus or a closely-related virus have been reported from Africa; and Australian bat lyssavirus seems to be limited to Australia. 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 post-exposure prophylaxis. When it first enters the host, this virus replicates outside the nervous system (e.g., in muscle), a stage called the eclipse phase. There are no clinical signs during this time. After several days to months, the virus travels via peripheral nerves to the CNS, where it replicates and, reentering peripheral nerves, is distributed to highly innervated tissues. The highest concentrations of virus at this time are in nervous tissue, cerebrospinal fluid (CSF), salivary glands and saliva, though limited amounts of virus (or viral RNA) have been detected in a number of other tissues and organs, including ocular secretions. Rabies virus is not known to be shed in feces or urine.

Virus shedding differs between individuals: the amount of virus in saliva ranges from a trace to high titers, and an estimated 10-50% of infected animals may not shed the virus. Shedding can begin a few days and up to 2 weeks before the

onset of clinical signs, with the longest preclinical shedding reported in some studies in bats, skunks and dogs infected with certain variants. Little is known about transmission from birds; however, experimentally infected birds can shed live virus in saliva even with minimal or no clinical signs. The occurrence of asymptomatically infected mammals (dogs, bats) that shed virus but do not develop clinical signs has been proposed; however, this idea is very controversial.

Rabies is most often transmitted from animal to animal in a bite. It can also be acquired by other forms of contact with infectious saliva or neurological tissues, typically through mucous membranes or breaks in the skin. For instance, cases have been reported after touching saliva-contaminated wounds while assisting a person or animal that was bitten, or after placing a hand in the mouth of an infected animal. Rabies virus does not pass through intact skin. Handling most body fluids or intact organs from a rabies case is thought to be low risk, but needles or other sharp objects could theoretically transmit the virus if they penetrate neurons. Cases have also been seen in organ transplant recipients who receive tissues (e.g., corneas) or various internal organs from people with undiagnosed rabies.

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 can also be acquired by eating contaminated, uncooked tissues, and there is anecdotal evidence of transmission in milk to a lamb and a human infant from their mothers, though other routes could not be ruled out in the latter case. Some authors have speculated that the virus might spread between kudu either when they feed in a group on thorn trees or during mutual grooming. One case of apparent transplacental transmission to a human infant was documented in the Turkish-language literature.

Any species of animal can spread rabies, though carnivores tend to be more efficient vectors than herbivores. Transmission between humans has rarely been seen, probably in part because people with at-risk exposures are usually given post-exposure prophylaxis. However, one case occurred in a mother who had been bitten on the finger by her clinically ill son, and another in a child who had been repeatedly kissed by his infected mother during her illness.

Rabies viruses are rapidly inactivated by sunlight and desiccation, and do not survive long in the environment. However, infectious viruses may be recovered from tissues (e.g., brain) within carcasses for a time. Findings vary, but some studies detected live virus for up to a few days and possibly up to 2 weeks (at very low levels) at 24-35ºC (75-95ºF), for 20-22 days or longer at 10ºC (50ºF), and for 18 days at 4ºC (39ºF).

Rabies-related Lyssaviruses

There is little information on the transmission of rabies-related lyssaviruses, but it is probably similar to rabies. Infections 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. Other sick mammals (e.g., horses infected with ABLV) can also shed these viruses in saliva.

Disinfection

Rabies virus can be inactivated by a number of disinfectants including sodium hypochlorite, 70% isopropyl alcohol, ethanol, iodides, quaternary ammonium compounds, formaldehyde, phenol, VirkonS™ and some other agents. It is also inactivated by low (< 3) or high (> 11) pH and by UV irradiation.

Infections in Animals

Incubation Period

The incubation period in animals is usually around 2-3 weeks to 3 months, but it has been reported to range from a few days to 6 months, and even longer in rare cases.

Clinical Signs

The clinical course of rabies is usually a few days to about a week, though sudden death has also been seen. It is almost invariably fatal once clinical signs develop. The initial signs of illness may be vague, subtle and inconsistent, with fever and other nonspecific signs such as anorexia or an increased appetite, dehydration, vomiting, diarrhea and excessive salivation, as well as signs suggestive of neurological involvement (e.g., fearfulness, restlessness, temperament changes such as unusual aggressiveness or uncharacteristic affection, dilation of the pupils, hyperreactivity to stimuli). Pigs frequently have a very violent excitation phase at the onset of disease. Lameness in the injected leg is often the first indication of postvaccinal rabies from a live inactivated vaccine. After a few days, the neurological signs tend to develop into one of two forms, either paralytic or furious.

The paralytic ("dumb") form of rabies is characterized by progressive paralysis, though this may sometimes be preceded by a brief excitatory phase. Frequently observed signs in this form include paralysis of the throat and masseter muscles, and ataxia followed by ascending spinal paralysis or paresis. As the result of throat muscle paralysis, the animal may be unable to swallow, and it can salivate profusely. Laryngeal paralysis can cause changes in vocalization, including an abnormal bellow in cattle or a hoarse howling in dogs. Some animals develop facial paralysis or the lower jaw may drop. They may also become somnolent or depressed. Biting is uncommon in the paralytic form of rabies, and death is usually the result of respiratory failure.

The furious form is associated with infection of the limbic system and characterized by restlessness, wandering, howling, polypnea, drooling and unprovoked attacks on other animals, people or inanimate objects. Affected animals often swallow foreign objects such as sticks and stones. Cattle may appear unusually alert. Wild animals frequently lose their fear of humans and may attack humans or animals

they would normally avoid (e.g., porcupines). Nocturnal animals may be visible during the day. Some animals have convulsions, especially during the terminal stages, and death sometimes occurs during a seizure, but many animals eventually progress to incoordination and ascending paralysis that ends in death.

Despite these general patterns, the signs of rabies can be highly variable, and some 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 apparent, 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. Some infected rabbits developed obvious neurological signs, often of the paralytic form, but others had signs that were not initially suggestive of rabies, or only showed signs of a nonspecific illness before death. In one report, sudden death was the only sign in many infected squirrels.

Clinical cases in birds seem to be unusual, even in experiments where they were fed carcasses from rabid animals or parenterally inoculated with the virus. In one recent case, a chicken that died of rabies had a one-day history of anorexia and lethargy, a month after receiving a bite from a dog. Limited research on experimentally inoculated birds found that many had few or no clinical signs (e.g., mild behavioral changes) and recovered despite evidence for virus replication in the brain and/or virus shedding.

Rabies-related Lyssaviruses

Information about rabies-related lyssaviruses is currently limited to a small number of case reports and a few reports of experimental inoculation; however, the illness appears indistinguishable from rabies. Bats may either have mild or no clinical signs and survive the infection, or develop severe neurological signs and die.

Post Mortem Lesions

Rabies does not result in any characteristic gross lesions, though there may occasionally be hyperemia of the meninges or hemorrhages in the spinal cord, as well as lesions resulting from trauma, aspiration pneumonia or other consequences of neurological dysfunction. The stomach sometimes contains unusual objects (e.g., rocks, sticks) that were ingested. Histological lesions are most common in the brainstem, cerebellum, and spinal cord, but the distribution within these areas can vary between species. The typical microscopic lesions 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 is usually a postmortem diagnosis, most often made by detecting viral antigens in the brain at necropsy. Antigens can be widely distributed in the CNS when the clinical signs are advanced, but they are most common in the brainstem and may be limited to this site in the early stages. Antemortem diagnosis can be attempted by looking for viral nucleic acids or antigens in saliva, skin (tactile facial hair follicles) or the eye (e.g., corneal impression smears); however, negative antemortem tests are unreliable in ruling out rabies.

Rabies antigens are usually detected by immunofluorescence, but immunohistochemistry, ELISAs and commercial rapid antigen tests (e.g., lateral flow assays) may also be used. The rabies immunofluorescence test reacts with most rabies-related lyssaviruses, though it cannot distinguish any of these viruses from rabies. However, the current lateral flow assays for rabies are inconsistent in detecting rabies-related lyssaviruses. RT-PCR tests, including pan-lyssavirus assays as well as more specific tests, are employed occasionally in diagnosis, and can be particularly useful when the sample is small (e.g., saliva) or decomposed, or when large numbers of samples must be tested at one time.

Inconclusive results from a panlyssavirus RT-PCR test or immunostaining are usually investigated with other genetic tests and/or virus isolation in cell culture (e.g., mouse neuroblastoma cells). Live animal (mouse) inoculation can also be used for virus isolation, but this is now rarely done. The specific lyssavirus causing the illness can be identified with monoclonal antibodies, specific nucleic acid probes, or RT-PCR followed by DNA sequencing. However, pursuing clinical cases to this level is uncommon unless the circumstances of the exposure are suggestive. Histology to detect Negri bodies is nonspecific, and not recommended if more specific techniques are available.

Serology is occasionally used to test seroconversion in domestic animals before international travel, as well as in research. It is rarely useful for diagnosing clinical cases in animals, as the host usually dies before developing antibodies. Serological tests to detect vaccination responses include virus neutralization tests (VN) and ELISAs, though only VN tests are recommended for international travel. Serology cannot distinguish reactions to rabies virus and rabies-related lyssaviruses. Cross-reactions with most other rhabdoviruses are not a concern, though some cross-reactive epitopes have been reported in members of the *Ephemerovirus* genus (bovine ephemeral fever virus and closely related viruses).

Treatment

Rabies is almost always fatal once the clinical signs develop, regardless of any attempts at treatment, and rare survivors are usually left with serious neurological

dysfunction. For this and other reasons (e.g., the risk to humans), no treatment is attempted and rabid animals are euthanized. Post-exposure prophylaxis, as practiced in humans, has not been validated for animals and is often prohibited due to the potential risks to human caregivers (though this is not the case in all countries). However, revaccination of exposed, vaccinated animals placed under observation, which was formerly prohibited, is now allowed under National Association of State Public Health Veterinarians (NASPHV) rabies guidelines in the U.S.

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

Rabies prevention is based primarily on vaccination and the avoidance of contact with infected wildlife or domestic animals. Some common measures include preventing dogs and cats from roaming, and housing rabbits, rodents and other caged pets where they are unlikely to contact rabid animals (e.g., either indoors or in an elevated, double-walled hutch without 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. Most countries also have regulations to prevent the importation of infected animals, which may include quarantine and/or testing for vaccine-induced seroconversion.

Vaccines are licensed for dogs, cats, ferrets, some livestock and wildlife, and may occasionally be used extra-label in other species, such as animals in petting zoos. Puppies under 3 months of age should be included in mass vaccination campaigns in regions where the urban rabies cycle is still common and many dogs do not receive periodic vaccinations. Limited data suggest that their young age alone does not prevent them from responding to high quality inactivated vaccines with adequate rabies titers. Oral wildlife vaccines, targeted at virus reservoirs and other species important in the epidemiology of a variant, can significantly reduce the threat from this source. Oral vaccines have also been used in canine rabies control programs in countries with large stray dog populations. Rare cases of postvaccinal rabies have been reported with some parenteral modified live vaccines, and were also an issue with some earlier oral wildlife vaccines. However, this does not seem to be a significant issue with the current live oral vaccine (SAG2) used in Europe.

The disposition of a domestic animal exposed to rabies can be influenced by its species, vaccination status and location. In many countries including the U.S., authorities recommend that unvaccinated animals be euthanized so that their brain may be tested for rabies. This prevents unnecessary prophylaxis in people who may have been exposed, and also reduces the risk of exposure for caretakers. If the owner is unwilling to allow euthanasia, an exposed animal in the U.S. may be placed in strict isolation for 4-6 months, depending on its species. Vaccinated animals in the U.S. are usually revaccinated and confined under observation for 45 days. Recommendations from the NASPHV now indicate that animals with expired vaccinations should be treated similarly to vaccinated animals.

Rabies-related lyssaviruses

Good quality rabies vaccines appear to provide adequate protection against other viruses in phylogroup I (e.g., EBLV 1 and 2, Australian bat lyssavirus); however, research suggests that efficacy against some viruses may require higher antibody titers. The current rabies vaccines do not seem to be sufficiently effective for viruses in other phylogroups. Bats that are sick or behaving abnormally are more likely to be shedding rabies-related lyssaviruses, but infections can also be acquired from apparently healthy bats.

Morbidity and Mortality

Rabies tends to be a sporadic disease that occurs in individual cases and small clusters, but larger outbreaks or epizootics can occasionally be seen, either as the result of common source exposure (e.g., cattle herds bitten by vampire bats,) or from rabid animals propagating viruses. Although the latter is more likely among carnivores, it has been seen even among ungulates, particularly kudu in Africa, which have experienced at least two major epizootics since the 1970s. The incidence of rabies is influenced by vaccination rates as well as exposure. Cases are now sometimes more common in cats than dogs where the urban rabies cycle has been controlled, probably due to lower vaccination rates combined with greater exposure to wildlife.

Rabies is almost always fatal once the clinical signs appear, and rare survivors from experimental infections (e.g., one ferret, a few dogs, mice and rabbits) are usually left with serious neurological deficits. However, exposure does not always result in clinical signs. Studies have estimated that rabies develops in approximately 50% of dogs and 10% of vampire bats exposed to this virus. Antibodies to rabies or related lyssaviruses have also been found in diverse wild canids, felids and hyaenids, and other wild and domestic animals, suggesting that some encounters might not result in disease. Factors that may affect the outcome include the virus variant, its presence in saliva at the time of the bite, dose of virus, route and location of exposure, and host factors such its species, age and existing immunity to lyssaviruses.

Clinical cases and deaths seem to be very rare in birds. Though only a few studies have been done, experimentally infected birds often had few or no clinical signs and survived, even in cases where viral replication was demonstrated.

Serological surveys have reported conflicting results, with some finding antibodies in owls, raptors, crows and other birds that might occasionally eat tissues from rabid animals, while others (which may have used more specific tests) reported no significant seropositivity in these birds.

Rabies-related Lyssaviruses

Although some rabies-related lyssaviruses seem to be relatively common in bats, only a few clinical cases have been reported in domestic animals. All of these cases, as well as experimental infections in mice, sheep, foxes, ferrets, dogs and cats inoculated with EBLV-1, and dogs and cats inoculated with Irkut virus, were fatal. Some experimentally infected bats also developed severe neurological signs and died, while others remained asymptomatic or had milder clinical signs and survived. Unusual clusters of neurological disease caused by Australian bat lyssavirus have been reported in groups of 4-9 week old flying fox pups, which do not yet fly and may be attacked by a rabid adult bat.

Infections in Humans

Incubation Period

The incubation period for rabies is reported to range from a few days to more than a year in humans, but most cases become apparent in a few weeks to about 3 months. The incubation period for rabies-related lyssaviruses may be similar.

Clinical Signs

Nonspecific prodromal signs may be apparent for up to about 10 days in the early stages, and may include fever, malaise, headache, sore throat and gastrointestinal signs, as well as discomfort, pain, pruritus or other sensory alterations at the site of virus entry. The neurological signs of rabies include behavioral and sensory changes as well as motor deficits, and may initially be subtle. They can include anxiety, insomnia, confusion, agitation, abnormal behavior, delirium or hallucinations; hypersensitivity to light, sound, air movements or other stimuli; ataxia, paralysis or paresis; hypersalivation, difficulty swallowing, pharyngeal spasms upon exposure to liquids; and convulsions. Either an encephalitic (furious) form with hyperexcitability, autonomic dysfunction and hydrophobia, or (less often) a paralytic form characterized by weakness progressing to generalized flaccid paralysis, may predominate. There are also cases with atypical signs.

Rabies is almost always fatal. Death usually occurs within 2 weeks; however, the paralytic form tends to be more prolonged than the encephalitic form, and some patients have survived for months with supportive care before finally succumbing. The rare survivors are most often left with severe neurological deficits, though there are a few documented cases where patients recovered well, with few or no sequelae. Some full-term infants have been born alive and healthy from pregnant women with clinical rabies.

Rabies-related Lyssaviruses

There are only a few reports of illnesses caused by rabies-related lyssaviruses, but they were similar to rabies. Nearly all of these cases were fatal.

Diagnostic Tests

It is sometimes possible to diagnose rabies by detecting viral nucleic acids or, less often, antigens or live virus, in saliva, throat swabs, skin biopsies taken from the nape of the neck (cutaneous nerves at the base of the hair follicles), corneal impressions, eye wash fluid, CSF or brain biopsy samples. These tests are most likely to be positive during the first week of illness, and their sensitivity varies with the test and sample. For instance, immunofluorescence on corneal smears is reported to be very insensitive, while repeated sampling of saliva is more likely to be diagnostic. More than one test may be necessary, as the virus is not invariably present in any tissue other than the CNS. Postmortem diagnosis is based on detecting the virus in the brain, as in animals.

Serology can be employed in humans, though it is mainly useful in patients who survive for at least 1-2 weeks. Positive CSF samples are particularly valuable, as they indicate that the virus is replicating in the CNS. The interpretation of seropositive blood samples is complicated by factors such as the use of vaccines in post-exposure prophylaxis and the occasional detection of anti-rabies antibodies in healthy people.

Rabies is usually undetectable during the incubation period.

Treatment

Post-exposure prophylaxis (PEP), given to people who have been exposed but not yet developed clinical signs, is very successful in preventing rabies. Failure of adequate PEP has been reported, typically in people who received a bite in a highly innervated area such as the face, but it is rare. Full-term infants born to pregnant women with clinical rabies are also given PEP. Rabies PEP appears to be effective in people exposed to other phylogroup I viruses (e.g., ABLV, EBLV-1), but its efficacy against other viruses may be limited.

PEP normally consists of immediate wound cleansing to remove as much contamination as possible, followed by the administration of human rabies immunoglobulin or licensed monoclonal antibody products and multiple doses of human rabies vaccine. Some countries may recommend both immunoglobulin and vaccination, regardless of the type of exposure; others recommend only the vaccine in case of low risk exposures, such as a minor abrasion or scratch without bleeding from an animal other than a bat. Routine (pre-exposure) vaccination eliminates the need for rabies immunoglobulin, even after a serious exposure, and reduces the number of vaccine doses needed. However, it does not completely eliminate the need for PEP.

Once a patient develops symptoms, no treatment is known to consistently influence the outcome. Patients may be offered either an aggressive approach (treatment in a

critical care facility that may include antiviral agents, immunotherapy and neuroprotective therapy) or a palliative course (e.g., sedation, tranquilizers, analgesics as needed). Only a small percentage of survivors have recovered adequately using either approach. It is possible for aggressive treatment and intensive care to prolong life without influencing the outcome, and some patients may remain in a vegetative state for months before dying.

Control

Controlling rabies in domestic and wild animals, mainly through vaccination, reduces the risk to humans. Wild animals should not be handled or fed, and 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, handling raw tissues is risky; rabies cases have been reported in people who butchered and cooked rabid animals for food.

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. Bites are generally the greatest danger from pets, but livestock may also kill or cause serious injury due to their size. 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 there may be exposure to infectious tissues. 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.

Recommendations for PEP after an animal bite are influenced by 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. In the U.S., asymptomatic dogs, cats or ferrets that have bitten humans are confined under observation for a short period, e.g., 10 days. If the animal develops signs of rabies during this time, it is euthanized and tested. Other types of exposures to a potentially rabid animal and contacts with bats (e.g., finding a bat in a room with a sleeping person) should also be reported immediately so that they may be evaluated and any necessary PEP begun promptly.

Inactivated human vaccines are available for veterinary staff, other animal handlers, wildlife officers, laboratory workers, international travelers in high risk regions, and others at high risk of exposure. People in high risk occupations should have their antibody titers monitored periodically, with revaccination as needed. Vaccination does not eliminate the need for PEP, as a vaccinated person may still develop rabies, but fewer treatments are needed. It may also provide some protection if the person is unaware of the exposure or PEP is delayed. All currently licensed vaccines are based on rabies virus; however, they appear to provide some protection against other phylogroup I viruses.

Morbidity and Mortality

The risk of developing rabies is influenced by a person's occupation, recreational activities and geographic location, as well as the availability of adequate healthcare. Clinical cases have become uncommon in countries where canine rabies has been controlled or eliminated and effective post-exposure prophylaxis is readily available. As an example, 0-3 cases of rabies are usually reported annually in the U.S., where cases typically occur only in people who did not realize they were exposed, or for some other reason, did not seek medical treatment. However, human rabies is still a common disease in some parts of the developing world, where over 90% of cases may be caused by rabid dogs. Serological studies have reported that healthy people in some locations occasionally have antibodies to rabies virus, suggesting previous exposure without clinical signs.

Without PEP, an estimated 15-20% of people bitten by rabid dogs will develop rabies. Once the clinical signs develop, the disease is almost always fatal. There are only about 20 well-documented cases of survival, as of 2020, and few made a good recovery; most survivors had severe and debilitating neurological sequelae and a very poor quality of life. Most of the patients who recovered well, with relatively few residual neurological signs and little or no cognitive impairment, were young and in good health. Survival seems to be correlated with the early development of antibodies, though this alone does not necessarily predict recovery without severe sequelae. The outcome might also be influenced by other factors, such as the type/origin of the virus, i.e., exposure to a less virulent strain.

Rabies-related Lyssaviruses

Infections with rabies-related lyssaviruses seem to be rare, but might be underdiagnosed, as the symptoms are identical to rabies and many of the commonly used tests do not distinguish these viruses. Almost all reported cases have been fatal. One of two children thought to have been infected with Mokola virus recovered, though there is some question whether this child was actually infected with the virus. 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. As with rabies, there is some evidence that people in regular contact with reservoir hosts may occasionally be seropositive.

Internet Resources

Compendium of Animal Rabies Prevention and Control

Jarvis JA et al (New York State Department of Health). Rabies Necropsy Techniques in Large and Small Animals. J Vis Exp. 2019 Jul 30;(149)

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manualhttp://www.merckvetmanual.com/

World Health Organization. Rabies

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

WOAH Terrestrial Animal Health Code

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