Published in final edited form as:

Vet Clin North Am Small Anim Pract. 2008 July ; 38(4): 851–ix.

Rabies in small animals

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Introduction

Rabies is an ancient disease and its history can be traced back more than 5000 years ago²⁴. Despite significant scientific progress, rabies remains an important global disease. Annually, more than 55,000 human fatalities are reported, and millions of others require post-exposure treatment^{38,39}. Most of the human cases occur in the developing nations of Asia and Africa, where dog rabies remains endemic or epizootic and thus is the main source for human exposure²⁴. In developed countries, human rabies has dramatically declined during the past 60 years as a direct consequence of routine vaccination of pet animals.

Rabies in the United States

In the United States, rabies was endemic in small animals, particularly in dogs, and thus was a major public health problem in the beginning of the last century. About 10,000 rabies cases were reported annually in dogs and cats⁴³. Massive immunizations in domestic dogs and cats were initiated in the 1940s and 1950s. As a consequence, rabies in dogs and cats declined dramatically and now only a few hundred cases are reported each year⁴³ (Fig 1). The rabies virus strains that used to be associated with dogs have disappeared during the last few years¹³. Viruses associated with small animals are derived from strains affecting wildlife animals.

Currently wildlife rabies is enzootic in the United States. Seven to eight thousand cases have been reported in wildlife annually during the past two decades^{8,9}. Concurrently there are a few rabies enzootics occurring in the United States. The distribution of the terrestrial animal rabies epizootics is shown in Fig. 2⁴⁵. Raccoon rabies has been spreading during the 1980s and 1990s along the eastern seaboard¹⁷ and spreading westward in the new century⁷. Three different variants exist in striped skunks in longstanding reservoirs in California, the north central states, and the south central states¹⁶. Now skunks have been reported to be infected with raccoon and bat rabies variants in other states^{26,33}. There are at least three fox rabies enzootics: arctic foxes in Alaska, along with red and gray foxes in the southeast^{5,12}. Some of these terrestrial wildlife species may have acquired rabies virus from dogs a long time ago and have adapted to their own species and locations¹⁸. Others may have evolved from bat rabies variants³³. Spillover from one species to another occurs from time to time^{25,33} and may lead to spreading in the new species. The distribution of these terrestrial rabies epizootics are depicted in Fig. 2A and the phylogenetic relationship of these rabies variants in the United States is summarized in Fig. 2B⁴⁵. In addition to terrestrial animal rabies, bat rabies has been

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detected in all the 48 contiguous states and has been responsible for most of the human cases in the United States for the past 20 years⁸.

Wildlife rabies presents a health problem to domestic small animals, which in turn have a higher risk of transmission to humans due to their close contact with people. Rabies variants found in domestic animals include variants found in raccoons, north central skunks, south central skunks, Texas foxes, Texas dog-coyotes and California skunks³⁵.

Rabies in Dogs

Dogs are the natural host for rabies. There are two forms of rabies—the excitatory or "furious" form, and the paralytic or "dumb" form^{3,28}. There are several overlapping phases during the progression of the disease: the prodromal period, the furious period, and the paralytic period^{3,28}. However the clinical signs of rabies may vary among animals. The first stage lasts 2 to 3 days in dogs. During this phase, infected animals always show different behavior. The excitement phase may last up to a week, but sometimes animals progress directly from the prodromal phase to the paralytic stage. In the second period, animals suddenly become vicious and behave erratic. Within several days, the disease progresses to the paralytic period. In the last period, animals show paralysis first in the wound limb, and then in the neck and head. Disease in animals ends in respiratory failure and death^{3,28}. The course of rabies typically lasts 3 to 8 days in dogs.

Recently a report described rabies symptoms in a 6 month old mixed breed female dog in Florida, which provides valuable insight into clinical presentation of rabies meningoencephalomyelitis. At presentation, the dog has a 3 day history of acute paraplegia, including areflexia, hyperesthesia, and non-painful swelling of the left second and third digits of the affected limb, eventually progressing to flaccid paralysis of the right pelvic limb. Analysis of lumbar CSF showed abnormally high protein, RBC, and WBC counts. Cytopathology revealed 78% lymphocytes, 21% mononuclear phagocytes, and 1% neutrophils. Serum testing for rabies neutralization antibodies using RFFIT assay was negative. EMG of left pelvic limb revealed moderate fibrillations and positive sharp waves suggestive of denervation/myopathy. No M wave could be generated for the left sciatic nerve, indicating a lack of axonal or neuromuscular transmission. F waves were also absent on the left sciatic, tibial and ulnar nerves. Results for the right limb, paravertebral muscles and thoracic limb muscles, and right sciatic, tibial and ulnar nerves were normal. Dementia, salivation and development of bilateral ventrolateral strabismus, focal and facial limb seizure and aggression occurred upon recovery from anesthesia. After euthanasia, the animal tested positive for raccoon rabies. Intracytoplasmic inclusion bodies could be seen in the brain stem and spinal cord. Degenerate and necrotic neurons were seen within thoracic and lumbar spinal cord⁶.

It is interesting to note that there have been cases of cerebral cysticercosis caused by the larval *Taenia solium* which mimics rabies virus infection in dogs⁵¹. Additionally, there have been cases of cutaneous vasculitis associated with rabies vaccine administration in dogs, all with a similar inflammatory pattern of mononuclear cells (nonleukocytoclastic)⁴⁰.

Rabies in Cats

Cats are the domestic animals most frequently reported rabid in the United States, and 200 to 300 cases are reported annually³¹. In one study in Pennsylvania, 44% of human post exposure prophylaxis (PEP) were due to exposure to a potentially rabid cat²⁵. Factors influencing the increased incidence of rabies in cats include community tolerance of free ranging felines, as well as less frequent rabies vaccination due to more lenient state laws for cats as compared to dogs. Additionally, communities of feral cats exist, and people who care for these feral animals are at risk for coming into contact with rabies virus. Cats are predominantly affected by the

variant of rabies virus endemic to the region in which they reside. For example, along the North American East coast, cats are commonly infected with raccoon rabies virus variant. However, cats can also contract bat rabies virus variants, as both cats and bats are nocturnal, and cats trap small animals such as bats²⁷. Rabid cats display symptoms similar to those in dogs, but have a tendency to hide in secluded places and are often more vicious. Similar to recommendations for dogs, it is a common recommendation to confine and observe a cat involved in a human bite, in order to rule out rabies exposure^{27,53}.

Rabies in other small animals

In addition to dogs and cats, rabies has been reported in other domestic small animals such as ferrets and rabbits. Two species of ferrets are common in the United States, the common ferret (*Mustela putorius*) and the black-footed ferret (*Mustela nigripes*). Ferrets have become popular companion animals in the United States. Ferrets were originally used to hunt small game and suckling animals, and may be attracted by the smell of milk⁴⁹. Although rare, rabid pet ferrets have been reported in the United States¹³. Therefore, it has become increasingly important to be aware of clinical signs of rabies in domestic ferrets, to avoid potentially harmful interactions with their human owners. Clinical signs of paralytic rabies in ferrets included lethargy, ataxia, paresis, paraparesis, paralysis, bladder atony, constipation, hypothermia, inappetence and anorexia, abnormal or frequent vocalization, sneezing, parasthesia, and ptyalism (moist or matted fur around the mouth). Only about 10% of rabid ferrets in experimental infection showed aggressive behavior with rapid attack and destruction towards a paper applicator, most had no to mild interest in the applicator. It has been recommended to vaccinate all pet ferrets against rabies, and to consider rabies in the differential diagnosis of ferrets with acute personality change and/or paralysis^{41,42}.

Rabies cases have also been reported in both rodents and lagomorphs, including a rabid pet guinea pig in 2003 which bit its owner in the clavicle. The guinea pig was later found to be infected with raccoon rabies virus. Between 1991 and 2001, the Wadsworth Center Rabies Lab received 7 lagomorphs, all pet domestics, 3 of which were exposed to a raccoon and 1 to a skunk. All 7 lagomorphs were infected with raccoon rabies virus²³. However, rodents and lagomorphs should be considered “spillover” species, not reservoirs. Unfortunately often times no clinical signs are obvious in rabies-infected rodents. In 1972, a study on rabid squirrels showed that ½ of infected animals that died of rabies showed no clinical signs^{23,57}.

Two cases of rabies in domestic rabbits (*Oryctolagus cuniculus*) in Maryland in 1999 are worth note here. In both of these cases rabbits were sent home with owners after examination, and owners were instructed to hand or force feed rabbits which later died and were found to be rabid. Clinical signs of illness in these rabbits upon examination included weakness in forelimbs, palpable subcutaneous crepitus, slight intermittent head tremors, ear infection, nasal discharge, and anorexia. Upon readmission one rabbit exhibited heavy wheezing, inability to stand, head tilt, and bilateral conjunctivitis. The disease course culminated in a recumbent and non-responsive state. The case history of this rabbit included an attack by a raccoon in a rabies endemic area resulting in a wound to the ear and the rabbit being covered in saliva²⁹. It is critical that rabies be considered in the differential diagnosis of any rabbit coming into contact with raccoons, especially those displaying neurological signs. Furthermore, discharging an animal that has been exposed to potentially rabid wildlife should be avoided, as should recommending owners to force feed these animals, bringing them in closer contact to a potentially rabid pet.

Despite natural infection of rabbits being rare, it is imperative to remember that rabbits are used for rabies diagnostic testing, and were used for creation of the first rabies vaccine by Louis Pasteur in the 1880s. Rabbits are highly susceptible to rabies virus infection, have incubation

periods between 2 and 3 weeks after intracerebral inoculation, and usually develop paralytic rabies. Experimentally infected rabbits display anorexia, fever, restlessness, weight loss, and neurological signs such as teeth grinding, head tremors, poor coordination of the hind limbs, and ascending paralysis. The affected rabbit usually dies within 3–4 days²⁹. Veterinarians should advise patients that no rabies vaccine is available for rabbits, so prevention is essential. Rabbits should be kept indoors or kept in elevated hutches without exposed wire mesh floors, and rabbits should be supervised at all times when exercising outdoors²⁹.

Laboratory diagnosis for animal rabies

Clinical signs are good indication for rabies in small animals. However rapid and accurate laboratory diagnosis for animal rabies is important for confirmation. In addition, many animals may not show typical signs of rabies. Usually rabid or suspected rabid wild animals are road kill or otherwise deceased when brought into diagnostic laboratories. Laboratory diagnosis is very important because it provides not only data for epidemiological investigation of animal rabies, but also guidance for initiation of PEP in affected people¹⁴.

Direct florescent antibody assay (dFA)

The most frequently used method for rabies diagnosis in the laboratory is dFA^{420,21}. Usually, brain smears or brain imprints from rabid or suspected rabid animals are reacted with fluorescein isothiocyanate (FITC)-conjugated-anti-rabies N antibodies^{4,55}. When observed under a fluorescent microscope, the green-fluorescent foci will show the rabies virus antigen (Fig. 3A). dFA is rapid, economical, and sensitive for laboratory diagnosis of animal rabies. Rabies antigens can be detected by the specific antibody; however, they should be differentiated from the non-specific background.

Direct rapid immunohistochemistry test (dRIT)

Recently, the CDC developed the dRIT³², which is similar to dFA. Brain smears or imprints on glass slides are fixed with 10% buffered formalin³². According to standard immunohistochemical staining, the virus antigen can be detected by anti-rabies N monoclonal antibody and examined under a light microscope. The sensitivity and specificity of dRIT is equivalent to that of the dFA³².

Virus Isolation

Mouse inoculation is a world health organization (WHO) recommended method to confirm dFA when the result is negative³⁰⁵⁶. Usually, brain suspension or spinal fluid from rabid or suspected rabid animals is intracerebrally inoculated into mouse brain. Two mice are killed every 2 days post infection until day 20 and brain smears are subjected to dFA. The 50% mouse intracerebral lethal dose (MICLD₅₀) can be calculated⁴⁶. Virus isolation can also be performed in cell culture, usually on neuroblastoma cells⁵⁹. The 50% tissue culture infective dose (TCID₅₀) can be calculated⁴⁶. Cell culture inoculation is as sensitive as the mouse inoculation test⁴⁷ and it requires less time to obtain results.

Reverse transcriptase Polymerase chain reaction (RT-PCR)

RT-PCR is a newly developed method for rabies diagnosis^{4,50}. RT-PCR is very useful when sample size is small such as saliva and spinal fluid. Viral RNA is amplified by RT-PCR with primers usually designed from the N gene, the most conserved gene in rabies virus. RT-PCR for rabies diagnosis is as rapid as dFA and is as sensitive as mouse inoculation test³⁴. RT-PCR is also widely used in epidemiological investigation and outbreak studies. When combined with sequencing, this method can also be used to differentiate rabies virus variants from

multiple species of animals^{19,35,50,54}. Viral variants can also be differentiated with different monoclonal antibodies in an indirect fluorescent antibody assay^{22,35}.

Histopathology and Immunohistochemistry

Rabies diagnosis in small animals can also be performed on brain tissues by histopathology and immunohistochemistry⁴⁴. Histopathology may show lymphocytic inflammation, perivascular cuffing, gliosis, and neurodegeneration⁵². Inflammation is diffuse in neuraxis. The parenchymal glial response is at first microglial but later mixed with astrocytes. Neurone degeneration is often not severe⁴⁸. The severity of inflammation may vary between animal species. Sometimes, a spongiform encephalopathy with vacuolation in the gray matter can be observed¹⁵. Negri bodies which are ovoid eosinophilic intracytoplasmic inclusions^{11,58} are a hallmark for rabies diagnosis. Yet Negri bodies are not found in all rabies cases⁵².

In fixed brain tissue, immunohistochemistry can be used to confirm diagnosis (Fig. 3B). By using the rabies specific antibody and avidin-biotin colorimetric detection system, the virus can be detected. Antigen-positive neurons can be found in the brain and spinal cord.

Detection of rabies virus-specific antibodies

Detection of specific antibodies can be used as diagnostic tools for rabies. There are many methods that have been developed to detect rabies-specific antibodies. Rapid fluorescent focus inhibition test (RFFIT) is the method used most often to detect virus neutralizing antibodies^{4,10}. ELISA has also been used to detect virus-specific antibodies when the ELISA plate is coated with rabies virus antigens^{36,37}. Since antibodies take several days to develop, this method is rarely used in diagnosis of animal rabies. Rather detection of virus-specific antibodies is often used in vaccination studies.

Rabies control in domestic small animals

Rabies control in small animals is by routine immunization with inactivated rabies virus vaccines, which have been approved for dogs, cats, and ferrets. First vaccination is carried out at three months of age and followed by a booster one year later. Subsequent immunization is carried out annually or triennially depending on the type of vaccines used¹. Recently a recombinant canarypox vaccine is licensed for cats with a similar immunization schedule². Currently, it is required by law that dogs and cats be vaccinated against rabies.

Conclusion

Rabies in small animals has been dramatically reduced in the United States since the introduction of rabies vaccination of domestic animals in the 1940s. As a consequence, the number of human rabies cases has declined to only a couple per year. During the last several years, dog rabies variant has almost disappeared completely. However, rabies in wildlife has skyrocketed. At the present, there are many concurrent rabies epizootics in wildlife in the US: raccoon rabies along the eastern seaboard, skunk rabies in the central states and California, arctic fox rabies in Alaska, and red and gray fox rabies in the southwestern states. In addition, bat rabies is endemic in the 48 contiguous states. Each wildlife species carries its own rabies variant(s). These wildlife epizootics present a constant public health threat as well as the danger of reintroducing rabies to domestic animals. Vaccination is the key to prevent both rabies in small animals and rabies transmission to humans.

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Fig. 1.

Cases of animal rabies in the United States, by year, 1955–2006.⁸ Courtesy of http://www.cdc.gov/rabies/docs/rabies_surveillance_us_2006.pdf

Fig. 2.

(A) Geographic distribution of the major terrestrial carnivore hosts of rabies virus variants. Each region is largely characterized by a unique rabies variant specific to a single carnivore host. (B) Neighbor-joining tree for nucleotide sequence of a 320-bp region of the nucleoprotein gene of selected RABV isolates from the United States, Mexico, and Canada. Each group of virus isolates that was sequenced to illustrate the unique RABV variants associated with terrestrial carnivores is boxed. The Polar Fox variant (Arctic and red fox) is no longer considered enzootic in the United States. Bootstrap values are shown at the branching point for clades recovered in .700/1000 iterations of the data. ABLV was used as the outgroup and to root the tree. Samples from a rabid fox in Ontario, Canada (CN OT FX 2/4), and from two human rabies cases with exposures to rabid dogs in Mexico (MX/TX HM 1976 and 1979) are included to show variants of RABV shared across international boundaries. U.S. samples are identified by a two-letter abbreviation for the state and animal from which the sample originated, followed by the year the case occurred. With the exception of the Canadian sample (GenBank accession U11735), all RABV sequences were derived from samples in a virus repository at CDC. (Taken from Real et al⁴⁵)

Fig. 3.

Detection of rabies virus antigens by dFA (A) and immunohistochemistry (B). The virus foci show positive stains with green-fluorescent color (A). Courtesy of <http://www.cdc.gov/rabies/diagnosis.html>. The paraffin embedded slide was stained by anti-RV nucleoprotein monoclonal antibody 802-2. Rabies antigens in the cytoplasm and inclusions are shown in brown (using diaminobenzidine as the substance) and the cell nuclei are shown in blue (B).