

# Update on rabies

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Rabies remains an important public health problem worldwide due to endemic dog rabies in developing countries. Rabies was a re-emerging disease in the United States during the 1990s due to bat rabies virus variants. Australian bat lyssavirus also emerged in Australian bat populations and caused two human deaths. There have been important recent advances in our knowledge of the pathogenesis of rabies and in our ability to diagnose and prevent it. *Curr Opin Neurol* 15:327–331. © 2002 Lippincott Williams & Wilkins.

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## Abbreviations

<b>CNS</b>	central nervous system
<b>CSF</b>	cerebrospinal fluid
<b>LC8</b>	10-kDa cytoplasmic dynein light chain

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## Introduction

Rabies remains an important public health problem in the world due to uncontrolled dog rabies in developing countries. Globally there are over 30 000 reported human cases of rabies each year [1], although the actual number of cases is probably much higher. During the 1990s rabies became a re-emerging disease in the United States [2] and a rabies-related virus, Australian bat lyssavirus, emerged in bat populations and caused two human deaths in Australia [3]. In 2000 five humans died of rabies in the United States [4•] and one in Canada [5•]; one human died of rabies in the United States during 2001. Control of rabies in wildlife with oral immunization has shown success in some rabies vectors and holds promise for other vectors in the future. Recent developments in our understanding of rabies and advances in combating the disease will be reviewed.

## Pathogenesis

The pathogenesis of rabies has recently been reviewed [6,7]. There is a long incubation period in rabies usually lasting 30–90 days, but sometimes it lasts longer than 1 year [8]. During this incubation period a delay in the movement of rabies virus likely occurs at the site of inoculation, and infection of muscle fibers may be an important step after intramuscular inoculation of rabies virus [9]. Rabies virus binds to nicotinic acetylcholine receptors at the neuromuscular junction [10], and recent studies using nerve–muscle cocultures indicate that the neuromuscular junction is the major site of entry into neurons [11]. There is also recent evidence that the neural cell adhesion molecule [12] and the low-affinity p75 neurotrophic receptor [13,14] and perhaps also the *N*-methyl-D-aspartate NR1 receptor [15••] are rabies virus receptors. However, the relative importance of each of these putative receptors has not yet been clarified.

Rabies virus spreads in peripheral nerves and in the central nervous system (CNS) within axons by fast axonal transport at a rate of 12–100 mm per day [16–18]. Two recent reports have provided evidence that the rabies virus phosphoprotein (particularly involving amino acid residues at positions 143 and 147 [19]) interacts strongly with the 10-kDa cytoplasmic dynein light chain (LC8), which is a component of both cytoplasmic dynein and myosin V and is important in both microtubule-directed organelle transport and in actin-based vesicle transport in axons [20,21]. Mutants with a deletion in amino acid residues of the phosphoprotein encompassing a conserved LC8-interacting motif and simultaneous

substitution of the arginine at position 333 of the glycoprotein showed neuroattenuation in mice [22••]. Interestingly, mutants with deletions in the LC8 binding region of the phosphoprotein remained as pathogenic as their parent virus after intramuscular inoculation of suckling mice, indicating that the LC8 is actually dispensable in young mice for the spread of pathogenic rabies virus from a peripheral site to the CNS [22••]. Rabies virus has been used as a neuroanatomical tracer in order to define circuits of synaptically-linked neurons in rodents and primates, and these in-vivo studies have provided evidence that axonal transport of rabies virus occurs exclusively in the retrograde direction [23,24•]. After the development of CNS infection there is centrifugal spread (away from the CNS) of rabies virus, particularly involving the parasympathetic nervous system, to multiple organs in rabies vectors and humans [25]. Rabies virus prominently infects neurons, although infection of non-neuronal cell types has been recognized in the CNS (e.g., Bergmann glia [26]) and extraneural organs, including acini of salivary glands in rabies vectors.

Natural rabies is normally characterized by relatively mild neuropathologic changes in the CNS, supporting the idea that neuronal dysfunction must play an important role in producing the disease [6,7]. In-vivo studies by Prosniak and co-workers [27•] in mice have shown that experimental rabies virus infection resulted in down-regulation of about 90% of genes in the normal brain at more than 4-fold lower levels by using subtraction hybridization. Only about 1.4% of genes became up-regulated, including genes involved in regulation of cell metabolism, protein synthesis, and growth and differentiation. However, this study was not done in a natural model using wild-type (street) rabies virus, which is associated with much less neuronal cell death. Hence, the significance of the results to the pathogenesis of natural rabies is uncertain.

Koprowski and co-workers have hypothesized that nitric oxide neurotoxicity may mediate neuronal dysfunction in rabies, and they found induction of inducible nitric oxide synthase mRNA and increased quantities of nitric oxide in brains of experimentally-infected rabid rodents compared with uninfected controls [28,29]. Ubol *et al.* [30] have reported that treatment of mice with the inducible nitric oxide synthase inhibitor aminoguanidine delayed the death of rabid mice by 1.0–1.6 days (depending on the dose) compared with controls. Because nitric oxide also has antiviral activity, the role of nitric oxide in rabies pathogenesis needs further study.

### Clinical disease

In the United States a diagnosis of rabies is frequently not considered until relatively late or not

at all during the clinical course, which often results in failure in timely initiation of appropriate isolation procedures (i.e., wearing of gloves) and a need for postexposure rabies prophylaxis of multiple health care workers. In the United States there is frequently no history of an animal bite or other rabies exposure, because many of the cases are due to unrecognized exposures from bats (see below). There are early non-specific prodromal symptoms that may be followed by paresthesias, pain, or pruritus at the site of the healed bite wound. About 80% of rabies cases have the classic form of the disease and 20% have a paralytic form of the disease (dumb rabies). Consciousness is preserved in rabies until much later in the clinical course than in most other viral encephalitides. In classic disease there are periods of hyperexcitability separated by lucid periods and autonomic dysfunction is common. Hydrophobia with contractions involving the diaphragm and other inspiratory muscles is a characteristic clinical feature in 50–80% of patients. Limb weakness occurs early and is prominent in paralytic rabies, and sphincter involvement and cerebrospinal fluid (CSF) pleocytosis may be present. Paralytic rabies may be misdiagnosed as the Guillain-Barré syndrome. Death usually occurs within a few days even despite aggressive therapy in a critical care setting. Multisystem organ failure is common. There are only four well-documented survivors of rabies, and each of these individuals received rabies immunization prior to the onset of the disease [31•,32].

### Investigations

Magnetic resonance imaging of the brain in rabies patients may be normal or show multifocal lesions in the brainstem and hypothalamus. Pleasure *et al.* [33•] studied a human case and found high signals on T2-weighted images in the medulla, pontine tegmentum, and hypothalamus and only minimal gadolinium enhancement in these areas. In another case Awasthi *et al.* [34] reported hyperintense signals on T1 and T2-weighted images in the basal ganglia and thalamus, but not in the brainstem.

Neutralizing antibodies against rabies virus are not often detectable until the second week of clinical illness, and are, therefore, not very useful in antemortem diagnosis of rabies. Detection of rabies virus antigen in nuchal skin biopsies, corneal impression smears, and diagnostic brain biopsies (rarely performed) may confirm a rabies diagnosis. Detection of rabies virus RNA using reverse transcriptase–polymerase chain reaction amplification in saliva, CSF, and skin biopsies has been an important advance in rabies diagnosis [2]. The clinical utility of nucleic-acid sequence-based amplification on saliva and CSF specimens in the rapid diagnosis of rabies needs confirmation [35].

## Epidemiology

During the 1990s there was a re-emergence of human rabies in the United States due to rabies virus infection of insect-eating bats, and bat rabies is diagnosed in every state except Hawaii [36]. Between 1990 and 2001 there were 33 cases of human rabies in the United States; 8 were imported (all transmitted from dogs) and 25 were acquired indigenously. Twenty-four of these cases were attributed to rabies virus variants associated with bats and 71% (17/24) of the bat rabies virus cases were caused by a variant associated with Silver-haired (*Lasiomycteris noctivagans*) and Eastern Pipistrelle (*Pipistrellus subflavus*) Bats [2,37–40]. Only two of these 17 cases had a history of being bitten by a bat. Silver-haired Bats are small bats and produce very mild bite injuries [41•], and it is likely that bites may not be recognized unless they are witnessed. The bat rabies virus variant associated with Silver-haired Bats has biologic properties that may allow efficient replication in non-neuronal cells such as fibroblasts after inoculation in superficial tissues [42,43]. Domestic animals probably play no significant role in transmission of bat rabies viruses to humans, and only one bat-associated variant (associated with Big Brown Bats [*Eptesicus fuscus*]) was found in a cat among 78 dogs and 230 cats with rabies during 1999 [44•].

Australian bat lyssavirus is a rabies-related virus that was first isolated in a fruit-eating bat, the Black Flying Fox (*Pteropus alecto*) in Australia in 1996 [45], and has been identified in species of both fruit and insect-eating bats in Australia [46••]. This virus was responsible for two fatal human cases in 1996 and 1998, and both had exposures in 1996 [3]. It is unclear whether this bat virus is also distributed in Asia.

A large raccoon rabies epizootic has spread to involve eastern United States and north into Ontario and New Brunswick in Canada as well as west into Ohio [36,47]. There are efforts to limit the spread of raccoon rabies in geographic areas of the United States and Canada using intense wildlife vaccination campaigns [48,49]. Although passive surveillance has indicated thousands of raccoon rabies cases in the United States every year (2778 in 2000) [36], there has not yet been a human case of rabies due to the raccoon virus variant.

## Prevention

Rabies can be effectively prevented following a recognized exposure in humans with wound cleansing, active immunization with a modern cell culture rabies vaccine, and passive immunization by administration of human rabies immune globulin [50,51•]. Guidelines from the Advisory Committee on Immunization Practices are published periodically in the *Morbidity and Mortality Weekly Report* [50] and available on the Internet at [http://](http://www.cdc.gov/mmwr)

[www.cdc.gov/mmwr](http://www.cdc.gov/mmwr). Cell culture rabies vaccines are expensive to produce and are, unfortunately, out of reach to many people in developing countries where canine rabies is endemic. Nerve tissue vaccines are inexpensive, but they are associated with a high incidence of serious neurologic adverse reactions, including encephalomyelitis and the Guillain–Barré syndrome [52]. The world supply of human rabies immune globulin is limited and this product is expensive and not widely available in developing countries [53] and, at times, there is limited availability in developed countries. Equine rabies immune globulin is a cheaper and more widely available alternative in some developing countries, but adverse reactions occur more frequently with this product. Alternative approaches need to be developed for passive immunization of humans at risk. The use of a cocktail of human monoclonal antibodies or even a mouse monoclonal antibody may be a promising alternative, and the experimental utility of this approach has recently been explored *in vitro* [54,55•] and in an animal model [55•,56•].

Current Advisory Committee on Immunization Practices guidelines recommend initiation of postexposure rabies prophylaxis when there is a reasonable probability that a bat exposure may have occurred and the bat is unavailable for laboratory examination [50]. For example, a bat found in the room of an unattended small child or sleeping person is a situation for consideration of rabies postexposure prophylaxis. Some bat conservationists and researchers have raised objections to this policy [57], but no reasonable alternative has been offered to the working hypothesis that rabid bats occasionally transmit rabies virus to humans by undetected bites.

Rabies in wildlife is the main problem in North America and Europe. Control of wildlife rabies and also dog rabies by culling of host populations has usually proved futile due to the reproductive potential and resilience of the species [58•]. Oral vaccination programs involving aerial bait distribution methods have shown success in rabies control in Red Foxes in Europe and southern Ontario, in Gray Foxes in western Texas, and in coyotes in southern Texas [48,59,60•]. Vaccination programs against raccoon rabies, including trap–vaccinate–release programs and oral vaccination projects using a vaccinia–rabies virus glycoprotein recombinant virus vaccine, have recently been used [48,49]. However, it remains to be determined how effective they will be in controlling raccoon rabies in the United States and Canada. These programs are costly and they must be repeated on a regular basis until disease is eradicated. Oral vaccination of dogs may offer the best opportunity for the future control of rabies in many developing countries with endemic dog rabies.

## Conclusion

The rabies threat to humans is from dogs in developing countries and predominantly from insect-eating bats in the United States. The diagnosis of rabies needs to be considered early in a patient's clinical course in order to prevent multiple exposures of healthcare workers, and a history of an animal bite may be lacking. Further research is needed to better understand this ancient disease, to prevent human exposures by controlling rabies in animals around the world, and to successfully treat humans with rabies.

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