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## Rabies

### Issue Description

*Also known as "hydrophobia") is a viral zoonotic neuroinvasive disease that causes acute encephalitis (inflammation of the brain) in mammals. It is most commonly caused by a bite from an infected animal, but occasionally by other forms of contact. If left untreated in humans it is usually fatal. In some countries it is a significant killer of livestock.*

*The rabies virus makes its way to the brain by following the peripheral nerves. The incubation period of the disease depends on how far the virus must travel to reach the central nervous system, usually taking a few months. Once the infection reaches the central nervous system and symptoms begin to show, the untreated infection is usually fatal within days.*

*In the beginning stages of rabies, the symptoms are malaise, headache, and fever, while in later stages it includes acute pain, violent movements, uncontrolled excitements, depressions, and the inability to swallow water (hence the name hydrophobia). In the final stages, the patient begins to have periods of mania and lethargy, and coma. Death generally occurs due to respiratory insufficiency.*

*In non-vaccinated humans, rabies is usually fatal after neurological symptoms have developed, but prompt post-exposure vaccination may prevent the virus from progressing. Rabies kills around 55,000 people a year, mostly in Asia and Africa.*

### Transmission

Any mammal may become infected with the rabies virus and develop symptoms, including humans. Most animals can be infected by the virus and can transmit the disease to humans. Infected bats, monkeys, raccoons, foxes, skunks, cattle, wolves, dogs, mongoose (normally yellow mongoose) or cats provide the greatest risk to humans.

Rabies may also spread through exposure to infected domestic farm animals, groundhogs, weasels, bears and other wild carnivores. Rodents (mice, squirrels etc) are seldom infected.

The virus is usually present in the nerves and saliva of a symptomatic rabid animal. The route of infection is usually, but not necessarily, by a bite. In many cases the infected animal is exceptionally aggressive, may attack without provocation, and exhibits otherwise uncharacteristic behavior. Transmission may also occur via an aerosol through mucous membranes; transmission in this form may have happened in people exploring caves populated by rabid bats that will bite.

### Prevalence

The rabies virus survives in wide-spread, varied, rural fauna reservoirs. However, in Asia, parts of America and large parts of Africa, dogs remain the principal host. Mandatory vaccination of animals is less effective in rural areas. Especially in developing countries, pets may not be privately kept and their destruction may be unacceptable. Oral vaccines can be safely distributed in baits, and this has successfully reduced rabies in rural areas of France, Ontario, Texas, Florida and elsewhere, like in the City of Montréal (Québec) where baits are successfully used among raccoons in the Mont-Royal park area. Vaccination campaigns may be expensive, and a cost-benefit analysis can lead those responsible to opt for policies of containment rather than elimination of the disease.

There are an estimated 55,000 human deaths annually from rabies worldwide, with about 31,000 in Asia, and 24,000 in Africa. One of the sources of recent flourishing of rabies in East Asia is the pet boom. China introduced in the city of Beijing the "one-dog policy" in November 2006 to control the problem. India has been reported as having the highest rate of human rabies in the world, primarily because of stray dogs.

Rabies was once rare in the United States outside the Southern states, but raccoons in the mid-Atlantic and northeast United States have been suffering from a rabies epidemic since the 1970s, which is now moving westwards into Ohio. In the midwestern United States, skunks are the primary carriers of rabies, composing 134 of the 237 documented non-human cases in 1996. The most widely distributed reservoir of rabies in the United States, however, and the source of most human cases in the U.S., are bats.

## **Rabies and animals**

Rabies is infectious to mammals. Three stages of rabies are recognized in dogs and other animals. The first stage is a one to three day period characterized by behavioral changes and is known as the prodromal stage. The second stage is the excitative stage, which lasts three to four days. It is this stage that is often known as furious rabies due to the tendency of the affected dog to be hyperreactive to external stimuli and bite at anything near. The third stage is the paralytic stage and is caused by damage to motor neurons. Incoordination is seen due to rear limb paralysis and drooling and difficulty swallowing is caused by paralysis of facial and throat muscles. Death is usually caused by respiratory arrest.

Recently new symptoms of rabies of wild animals have been observed, namely in foxes. Probably at the beginning of the prodromal stage foxes, who are extremely cautious by nature, absolutely lose wild instincts. Animals come into settlements, reach for people, and behave as if tame. How long such "euphoria" lasts is not known. But even in such status the animal is extremely dangerous, as its saliva and excretions still contain the virus.

## **Prevention**

Almost every infected case with rabies resulted in death until a vaccine was developed by Louis Pasteur and Emile Roux in 1885. Their original vaccine was harvested from infected rabbits, from which the nerve-tissue was weakened by allowing to dry for five to ten days. Similar nerve tissue-derived vaccine are still used in some countries, as they are much cheaper than modern cell culture vaccines. The human diploid cell rabies vaccine (H.D.C.V.) was started in 1967, however a new and less expensive purified chicken embryo cell vaccine and purified vero cell rabies vaccine are now available. A recombinant vaccine called V-RG has been successfully used in the field of Belgium, France, Germany and the United States to prevent outbreaks of rabies in wildlife. Currently pre-exposure immunization has been used in both human and non-human populations, where as in many jurisdictions domesticated animals are required to be vaccinated.

## **Symptoms**

The period between infection and the first flu-like symptoms is normally two to twelve weeks, but can be as long as two years. Soon after, the symptoms expand to slight or partial paralysis, cerebral dysfunction, anxiety, insomnia, confusion, agitation, abnormal behavior, paranoia, terror, hallucinations, progressing to delirium. The production of large quantities of saliva and tears coupled with an inability to speak or swallow are typical during the later stages of the disease; this can result in "hydrophobia", where the victim has difficulty swallowing because the throat and jaw become slowly paralyzed, shows panic when presented with liquids to drink, and cannot quench his or her thirst. The disease itself was also once commonly known as hydrophobia, from this characteristic symptom. The patient experiences the response of "foaming at the mouth" as a result of the body's inability to quench its thirst; essentially, the overproduction of saliva as a last-resort attempt at retaining fluids.

Death almost invariably results two to ten days after the first symptoms.

## **Treatments**

### **Post-exposure prophylaxis**

Treatment after exposure, known as post-exposure prophylaxis or "P.E.P.", is highly successful in preventing the disease if administered promptly, generally within ten days of infection. Thoroughly washing the wound as soon as possible with soap and water for approximately five minutes is very effective at reducing the number of viral particles. "If available, a virucidal antiseptic such as povidone-iodine, iodine tincture, aqueous iodine solution or alcohol (ethanol) should be applied after washing." Exposed mucous membranes such as eyes, nose or mouth should be flushed well with water. In the United States, patients receive one dose of immunoglobulin and five doses of rabies vaccine over a twenty-eight day period. One-half the dose of immunoglobulin is injected in the region of the bite, if possible, with the remainder injected intramuscularly away from the bite. This is much less painful compared with administering immunoglobulin through the abdominal wall with a large needle, as was done in the past. The first dose

of rabies vaccine is given as soon as possible after exposure, with additional doses on days three, seven, fourteen, and twenty-eight after the first. Patients that have previously received pre-exposure vaccination do not receive the immunoglobulin, only the post-exposure vaccinations on day 0 and 3. Since the widespread vaccination of domestic dogs and cats and the development of effective human vaccines and immunoglobulin treatments, the number of recorded deaths in the U.S. from rabies has dropped from one hundred or more annually in the early twentieth century, to 1–2 per year, mostly caused by bat bites, which may go unnoticed by the victim and hence untreated.

In instances when post-exposure prophylaxis is administered as a precaution (e.g. a person wakes up and finds a bat in the room they were sleeping in), it is now mainly given in the gluteal region and deltoid (upper arm). The number of shots delivered to the gluteal area on the first day is determined by weight, and it is not uncommon to require three of these shots. Subsequent shots of the immunoglobulin (to build longer term immunity to rabies) are given to the arm. Recipients of the vaccine have reported that these shots are no more painful than normal shots (such as tetanus boosters).

Most official documentation on rabies on the internet and otherwise warn that treatment becomes futile with the onset of prodrome (when symptoms begin to appear). These texts are written to convince the layman not to delay seeking treatment (and rightly so). However, this may also lead them to falsely conclude that their situation is not an urgency and that treatment is possible up until the very end of the incubation period, as it may last 1 to 3 months on average; or it may at least convince them that it is safe to delay treatment by a few days. While the virus is treatable only during the incubation period, it is important to note that it is not treatable during its entirety. Rabies fully is treatable while the virus is present in tissues composed of cells other than neurons, such as skin and muscle. However, once the infection spreads to a neuron, the virus is sequestered from the immune system and will eventually make its way to the spinal cord and then to the brain. Treatment at this point may not be effective, even though symptoms may begin to appear weeks or even months later. Therefore, it is highly recommended that P.E.P. be administered as soon as possible. Begun without delay, or very little delay, P.E.P. is highly effective against rabies. In the case where there has been a significant delay in administering P.E.P., the treatment should be administered regardless of that delay, as it may still be effective if it is not too late.

## **Blood-brain barrier**

Some recent works have shown that during lethal rabies infection the blood-brain barrier (BBB) does not allow anti-viral immune cells to enter the brain, the primary site of rabies virus replication. This aspect contributes to the pathogenicity of the virus and artificially increasing BBB permeability promotes viral clearance. Opening the BBB during rabies infection has been suggested as a possible novel approach to treat the disease, even though no attempts have yet been made to determine whether or not this treatment could be successful.

## **Induced coma**

In 2005, local newspapers reported that Jeanna Giese (15) survived acute, unvaccinated rabies after being bitten by a rabid bat whilst attending Church. This indicates the successful treatment of rabies through induction of a coma, which was based on the theory that rabies' detrimental effects were caused by temporary dysfunctions of the brain, and that the induction of a coma (by producing a temporary partial stop in brain function) would protect the brain from damage while the body built up an immune response to the virus. After thirty-one days of isolation and seventy-six days of hospitalization, she was released from the hospital, having survived rabies.

Rodney Willoughby Jr., the primary care physician in this case (published in the April 2007 issue of Scientific American.), notes that subsequent failures of what he calls the Milwaukee protocol did not use the same cocktail of drugs used during the treatment of Giese. He notes the depletion of biopterin in the brain as a subject for future research.

Later attempts to use the same treatment have failed, but in April, 2008, in Cali, Colombia, local newspapers reported that an 11-year-old had recovered after induction of coma. This patient was infected on February 15, when several children were bitten by a cat in Santander de Quilichao, a small town near Cali. This claim has not been verified.

In November, 2008, a 15-year-old Brazilian boy was reported to have recovered from symptomatic rabies after using the Milwaukee protocol.

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