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Rabies: A Global Health Challenge

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Introduction:

Rabies is a severe and highly lethal zoonotic disease that causes viral encephalomyelitis and is present in the saliva of warm-blooded animals such as dogs, cats, jackals, and wolves. The disease is typically transmitted through the bite or lick of an infected animal. Vampire bats also significantly contribute to its spread.

Synonyms: Hydrophobia, Lyssa, Mad dog syndrome

Etiology:

The disease is caused by the rabies virus, a neurotropic virus belonging to the Lyssavirus genus in the Rhabdoviridae family. There are at least seven distinct genotypes of the rabies virus. Classical rabies virus, encompassing both street and fixed strains, is classified as genotype 1, serotype 1, within this genus. The street virus is found in naturally occurring cases, while the fixed virus is a laboratory-passaged, attenuated form used in vaccine production. The rabies virus is an enveloped, bullet-shaped RNA virus, typically measuring 75×180 nm. Its genome is composed of single-stranded, non-segmented, negative-sense RNA, which encodes five structural proteins: nucleocapsid (N) protein, phosphoprotein (P), matrix (M) protein, glycoprotein (G), and RNA-dependent RNA polymerase (L). Since the virus has an envelope, it is easily neutralized by a range of chemical disinfectants, as well as exposure to ultraviolet light, heat, and even sunlight.

Epidemiology:

More than 27,000 cases of animal rabies are reported yearly in the world. World Health Organization estimates that 55,000 to 100,000 human rabies cases occur annually, mostly in tropical countries of Asia and Africa. Rabid dogs are the main source of infection in people. Rabies virus transmission from dogs to people is intensified as the density of susceptible dogs exceeds 4.5 dogs/Km. As a result; approx. 10 million people annually receive post-exposure prophylaxis (PEP). Combined measures of immunocontraception and rabies vaccination have been proposed to help alleviate this zoonotic risk.

All warm-blooded animals are susceptible to infection with rabies virus, but mammals are the only known vectors and reservoirs in nature. Foxes, coyotes, jackals, wolves are among the most susceptible animal groups.

Skunks, raccoons, mongooses, bats, rabbits, cattle have a high susceptibility. Domestic dogs, sheep, goats, horses and non-human primates are moderately susceptible. Cats are even more resistant than dogs to canine rabies virus isolates but are much more prone to develop infection with field isolates from wildlife and with vaccine virus. Younger animals are usually more susceptible to rabies infection. Transmission always occurs via introduction of virus-laden saliva into tissues, usually by the bite of a rabid animal. However, the virus from saliva, salivary glands or brain can enter the body through mucous membranes or breaks in the skin; but is not transmitted through intact skin. Usually, saliva is infectious at the time clinical signs occur, but domestic dogs and cats may shed virus for several days even before onset of clinical signs. Hematogenous spread does not occur.

Aerosol transmission can also occur under very specialized conditions in which the air contained a high concentration of suspended particles or droplets carrying viral particles e.g. in a cave inhabited by millions of bats. Aerosol infection occurs via direct attachment of the virus to olfactory nerve endings. Human rabies is usually caused by a bite, but it has been acquired by corneal transplantation.

Incubation Period:

Ranging from week to months but in most cases 21-80 days after exposure. Rabies virus can remain viable in a carcass for several days at 20 ° C, although it may survive much longer when the body of the victim is refrigerated.

Pathogenesis:

Following bite, virus enters body through saliva and replicate in muscle cells or enters directly in peripheral nerves and binds with receptors for acetylcholine. After entry, virus start intra-axonal centripetal spread towards CNS through peripheral nerves. In spinal cord virus replicates in neurons and spreads rapidly throughout the nervous system, causing progressive lower motor neuron paralysis. In brain, virus affects neurons especially of hippocampus, cerebral cortex and brain stem. Then starts centrifugal journey towards salivary glands, skin, mucosal surfaces and most of the organs through peripheral and central nerves. Saliva becomes infective up to 2 weeks before appearance of symptoms.

Clinical Signs:

The incubation period is both prolonged and variable. It has been reported to be 3 to 24 weeks (average, 3 to 8 weeks) in dogs, 2 to 24 weeks (average, 4 to 6 weeks) in cats and 3 weeks to 1 year or more (average, 3 to 6 weeks) in humans. Unvaccinated animals had shorter incubation period and duration of clinical disease. The virus travels via the peripheral nerves (at the rate of up to 100 mm per day) to the spinal cord and ascends to the brain. After reaching the brain, the virus travels via peripheral nerves to the salivary glands from where the virus is shed intermittently in the saliva. Damage to the motor neurons causes progressive lower motor neuron (LMN) disease which produces the typical ascending flaccid paralysis.

Rabid animals of all species usually exhibit typical signs of CNS disturbance, with minor variations among species. The most reliable signs, regardless of species, are acute behavioral changes and unexplained progressive paralysis. Behavioral changes include sudden anorexia, signs of apprehension or nervousness, irritability and hyperexcitability (including priapism). Ataxia, altered phonation and changes in temperament are apparent. Uncharacteristic aggressiveness may develop in normal docile animal. The clinical course may be divided into three general phases – prodromal, acute excitative and paralytic/end stage. During the prodromal

phase, which lasts ~1–3 days, animals show only vague non-specific signs, which intensify rapidly. The term "furious rabies" refers to animals in which aggression (the acute neural excitative phase) is pronounced. "Dumb or paralytic rabies" refers to animals in which the behavioral changes are minimal and the disease is manifested principally by paralysis.

1. **Furious form** –

This is the classic "mad-dog syndrome," although it may be seen in all species. In dogs, this form usually last for 1-7 days. The animal becomes irritable and with the slightest provocation, may viciously and aggressively use its teeth, claws, horns or hooves. The animal is alert and anxious, with pupils dilated. Carnivores frequently roam extensively, attacking other animals including people and any moving object. Dogs may eat unusual objects (pica), especially wood. Young pups seek human companionship and are over-playful and may even bite when petted, usually become vicious in a few hours. As the disease progresses, muscular incoordination, disorientation and generalized seizures follows. If they don't die during seizure, may have a short paralytic stage before death.

2. **Dumb or Paralytic form** –

This usually develops within 1-10 days after first clinical signs noted and lasts 2-4 days which is manifested by ataxia and paralysis of the throat and masticatory muscles, often with profuse salivation and the inability to swallow. A change in the tone of the bark, resulting from laryngeal paralysis, may be observed. Dropping of the lower jaw is common in dogs. Mandibular and laryngeal paralysis is less common in cats. Increased frequency of vocalization is a common sign in cats. These animals may not be vicious and rarely attempt to bite. The paralysis progresses rapidly to all parts of the body, followed by coma and death in a few hours.

Species Variations:

- Among farm animals, **cattle** are most commonly affected. Average incubation period in cattle is 15 days and furious form occurs in 70% of cases. Major clinical signs are excessive salivation, behavioral change, muzzle tremors, bellowing, aggression, hyperesthesia or hyperexcitability and pharyngeal paralysis. In the paralytic form, knuckling of hind fetlocks, swaying of hindquarters while walking, deviation or flaccidity of tail to one side, are common early signs. Tenesmus with paralysis of anus, resulting in sucking in and blowing out of air, occurs late in incoordination stage just before recumbency. Death usually occurs 48 hours after recumbency develops and after a total course of 6-7 days.
- **In sheep**, average incubation period is 10 days and a number of animals are affected at one time due to ease with number of animals bitten by a dog. Clinical signs are similar to that in cattle.
- **Goats** are commonly aggressive and continuous bleating is common while in sheep, excessive bleating does not occur.
- **In horses**, average incubation period is 12 days and cases usually incline to paralytic form of disease. Muzzle tremors are most common initial signs, followed by pharyngeal paresis, ataxia or paresis of hindquarters, lethargy, recumbency and loss of tail and anal sphincter tone.
- **Pigs** manifest excitement, tendency to attack and incoordination. Affected sows show twitching of nose, rapid chewing movements, excessive salivation and colonic convulsions. Terminally, there is paralysis and death occurs 12-48 hours after onset of signs.

Laboratory Diagnosis:

- No ante-mortem diagnostic tests are sensitive enough to be consistently reliable for rabies diagnosis in animals. No hematologic or serum biochemical changes are characteristic for rabies. Increased CSF protein (110 to 150 mg/dl) and leukocytes (120 to 1140 cells/µl), with predominating small lymphocytes, have been reported in dogs with post-vaccinal rabies encephalomyelitis.
- No gross lesion in the CNS is detectable with rabies infection. Acute polioencephalitis is seen very early in the course of the disease, followed by necrotizing encephalitis in next phase of infection. Classic test for rabies is to examine the brain for the presence of intracytoplasmic inclusions, known as Negri bodies, in larger neurons. These are most common in neurons of the hippocampus in carnivores and in Purkinje's cells of herbivores. Negri bodies are best demonstrated with Seller's or Van Gieson's stains, in which they stain magenta.
- The definitive diagnostic test is the demonstration of rabies virus antigen by direct fluorescent antibody test (FAT) in suitable brain tissue. Thin touch impressions of the medulla, cerebellum or hippocampus are used for this test.
- Direct FAT of skin biopsy (nape of neck in humans and maxillary areas in animals) for viral antigen is a useful ante-mortem human diagnostic, but has not approved for diagnosis of rabies in animals.
- Detection of rabies virus antigen in dog's saliva by slide agglutination using latex particles coated with polyclonal immunoglobulin.
- Serological testing is used to determine vaccine immunogenicity. Tests to quantify specific rabies virus antibodies in serum include Rapid fluorescent focus inhibition test (RFFIT), ELISA and Fluorescent antibody virus neutralization (FAVN) test. A titer of 0.5 IU/ml is the standard level expected for an adequate titer in people and animals.

Treatment:

Supportive care for rabies-infected animals is not recommended because no therapy is effective in animals with this fatal encephalitis. An asymptomatic dog or cat suspected of contracting rabies should be quarantined or as for all other species, appropriately euthanized and the brain submitted for examination.

Prevention and Control:

The most appealing and effective control measures of rabies are centered on vaccination of dogs and cats with coverage of minimum 70% of the population. Inactivated tissue/cell culture vaccines are available and recommended for vaccination of animals. The dose in all animal species is 1 ml IM or SC.

Pre-exposure recommendations-

- Dogs and cats – Primary vaccination at 3 months of age; revaccinate annually.
- Other domestic species including cattle, sheep, horses – Primary vaccination at 3 months of age; revaccinate annually.
- Humans – Three dose regimen of an FDA-approved cell culture vaccine @ 1 ml IM in the upper deltoid on days 0, 7, and 21 or 28.

Post-exposure recommendations-

- Dogs and cats

- If previously unvaccinated – euthanize immediately or quarantine in secure enclosure for 6 months; vaccinate 1 month before release.
- Not currently vaccinated – evaluate on case-by-case basis.
- Currently/Routinely vaccinated – revaccinate immediately and keep under owner's control for 45 days.

- Other domestic animals including cattle, sheep, goat, horses
  - If unvaccinated – euthanize immediately or confine for 6 months and observe on case-by-case basis.
  - Currently vaccinated – revaccinate immediately and keep under observation for 45 days.
- Humans
  - Previously unvaccinated – H-RIG (Human rabies immune globulin) 20 IU/Kg, infiltrated at site of bite once on day 0–7; FDA-approved cell culture vaccines IM in upper deltoid on days 0, 3, 7 and 14.
  - Previously vaccinated – Three doses of an approved vaccine IM in upper deltoid on days 0, 7 and 21 or 28 days post-exposure with no H-RIG. With serologic evidence of an adequate titer or previous full PEP series, only two doses are needed on days 0 and 3 with no H-RIG.

Wound Care:

In cases of potential bites/scratches, wounds should be immediately washed thoroughly with 20% aqueous soap solution to reduce the chance of rabies virus infection. Ethanol (≥43%) or povidone-iodine solutions can be applied locally to open wounds.