Rabies (Lyssaviruses): The systematic Overview

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ABSTRACT:

Rabies is a zoonotic, fatal and progressive neurological infection caused by rabies virus of the genus Lyssavirus and family Rhabdoviridae. It affects all warm-blooded animals and the disease is prevalent throughout the world and endemic in many countries except in Islands like Australia and Antarctica. Over 60,000 peoples die every year due to rabies, while approximately 15 million people receive rabies post-exposure prophylaxis (PEP) annually. Bite of rabid animals and saliva of infected host are mainly responsible for transmission and wildlife like raccoons, skunks, bats and foxes are main reservoirs for rabies. The incubation period is highly variable from 2 weeks to 6 years (avg. 2–3 months). Though severe neurologic signs and fatal outcome, neuropathological lesions are relatively mild. Rabies virus exploits various mechanisms to evade the host immune responses. Being a major zoonosis, precise and rapid diagnosis is important for early treatment and effective prevention and control measures. Traditional rapid Seller's staining and histopathological methods are still in use for diagnosis of rabies. Direct immunefluoroscent test (DFAT) is gold standard test and most commonly recommended for diagnosis of rabies in fresh brain tissues of dogs by both OIE and WHO. Mouse inoculation test (MIT) and polymerase chain reaction (PCR) are superior and used for routine diagnosis. Vaccination with live attenuated or inactivated viruses, DNA and recombinant vaccines can be done in endemic areas. This review describes in detail about epidemiology, transmission, pathogenesis, advances in diagnosis, vaccination and therapeutic approaches along with appropriate prevention and control strategies.

Keywords: Rabies virus, Introduction, Etiology and Transmission, Pathogenesis, Epidemiology, Diagnosis, Prevention, Treatment, Review.

INTRODUCTION:

Rabies is a vaccine-preventable, zoonotic, viral disease affecting the central nervous system. Once clinical symptoms appear, rabies is virtually 100% fatal. In up to 99% of cases, domestic dogs are responsible for rabies virus transmission to humans. Yet, rabies can affect both domestic and wild animals. It spreads to people and animals via saliva, usually through bites, scratches or direct contact with mucosa (e.g. eyes, mouth or open wounds). Children between the age of 5 and 14 years are frequent victims. Rabies is present on all continents except Antarctica, with over 95% of human deaths occurring in Asia and Africa. However, rabies cases are rarely reported and registered numbers differ greatly from the estimated burden. Rabies is one of the neglected tropical diseases (NTD) that predominantly affects already marginalized, poor and vulnerable populations. Although effective human vaccines and immunoglobulin exist for rabies, these are often not readily available or accessible to those in need. Managing a rabies exposure, where the average cost of rabies post-exposure prophylaxis (PEP) is currently estimated at an average of US$ 108 (along with travel costs and loss of income) can be a catastrophic financial burden on affected families whose average daily income may be as low as US$ 1–2 per person. Every year, more than 29 million people worldwide receive PEP. This is estimated to prevent hundreds of thousands of rabies deaths annually. Globally, the economic burden of dog-mediated rabies is estimated at US$ 8.6 billion per year, in addition to uncalculated psychological trauma for individuals and communities.

ETIOLOGY AND TRANSMISSION:

Rabies virus and six additional rabies-related viruses, including Lagos, Mokola, and Duvenhage viruses, are members of the Rhabdoviridae family, genus Lyssavirus (which is derived from the Greek word lyssa, meaning “madness.” Rabies derives from the Sanskrit word rabhas, which means “to do violence.”) Rabies virus causes human encephalitis through zoonotic infection, predominantly by bats in the Americas.[1.] The lyssaviruses differ antigenically but are morphologically similar and neurotropic. [2.] Rabies virus is an

enveloped bullet-shaped virus, 180 nm long and 75 nm wide, composed of five structural proteins (Figure 228-1). It contains one copy of a single-stranded, nonsegmented, negative (noncoding) RNA of approximately 12,000 nucleotides. [3.]The virus envelope contains glycosylated G-protein spikes that bind to cells. The matrix (M) protein is located on the inner virus envelope, inside which the virus nucleoprotein (N) tightly binds the viral RNA to form the nucleocapsid core. This core, along with a large transcriptase protein (L) and a phosphorylated protein (P), is the rabies virus nucleocapsid (RNP).

Transmission:

Rabies virus is transmitted through direct contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth) with saliva or brain/nervous system tissue from an infected animal. People usually get rabies from the bite of a rabid animal. It is also possible, but rare, for people to get rabies from non-bite exposures, which can include scratches, abrasions, or open wounds that are exposed to saliva or other potentially infectious material from a rabid animal. Other types of contact, such as petting a rabid animal or contact with the blood, urine or feces of a rabid animal, are not associated with risk for infection and are not considered to be exposures of concern for rabies. Other modes of transmission—aside from bites and scratches—are uncommon. Inhalation of aerosolized rabies virus is one potential non-bite route of exposure, but except for laboratory workers, most people won't encounter an aerosol of rabies virus. Rabies transmission through corneal and solid organ transplants have been recorded, but they are also very rare. There have only been two known solid organ donor with rabies in the United States since 2008. Many organ procurement organizations have added a screening question about rabies exposure to their procedures for evaluating the suitability of each donor. Bite and non-bite exposures from an infected person could theoretically transmit rabies, but no such cases have been documented. Casual contact, such as touching a person with rabies or contact with non-infectious fluid or tissue (urine, blood, feces), is not associated with risk for infection. Contact with someone who is receiving rabies vaccination does not constitute rabies exposure, does not pose a risk for infection, and does not require postexposure prophylaxis. Rabies virus

becomes noninfectious when it dries out and when it is exposed to sunlight. Different environmental conditions affect the rate at which the virus becomes inactive, but in general, if the material containing the virus is dry, the virus can be considered noninfectious.

Animal Reservoirs:

Any mammal can get rabies. The most common wild reservoirs of rabies are raccoons, skunks, bats, and foxes. Domestic mammals can also get rabies. Cats, cattle, and dogs are the most frequently reported rabid domestic animals in the United States. You should seek medical evaluation for any animal bite. One important factor in deciding if you should have post exposure prophylaxis will be if the animal can be found and held for observation.

Animal Type	Evaluation and Disposition Of Animal	Postexposure Prophylaxis Recommendations
Dogs, cats, and ferrets	Healthy and available for 10 day observation	Persons should not begin vaccination unless animal develops clinical signs of rabies
	Rabid or suspected rabid	Immediately vaccinate
	Unknown (escaped)	Consult public health officials
Raccoons, skunks, foxes, and Bats	Regarded as rabid unless animal is proven negative by laboratory test	Consider immediate vaccination
Livestock, horses, rodents, rabbits and hares, and other mammals	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require rabies postexposure prophylaxis.

PATHOGENESIS AND CLINICAL PRESENTATION:

After inoculation, rabies virus may enter the peripheral nervous system directly and migrates to the brain or may replicate in muscle tissue, remaining sequestered at or near the entry site during incubation, prior to central nervous system invasion and replication. It then spreads centrifugally to numerous other organs. The case: fatality ratio approaches unity, but exact pathogenic mechanisms are not fully understood.

Rabies virus is inoculated into muscle and subcutaneous tissues in the saliva of a biting animal (Figure 1). There is a delay in movement of the virus at the site of inoculation during the incubation period that lasts for weeks to months. Rabies virus binds to nicotinic acetylcholine receptors at the neuromuscular junction and travels toward the spinal cord within axons of peripheral nerves by retrograde fast axonal transport at a rate of approximately 50–100 mm per day. The virus disseminates within axons in the CNS along neuroanatomical pathways. Rabies virus replicates in neurons and causes neuronal dysfunction by uncertain mechanisms, which is likely responsible for the clinical features and fatal outcome of the disease. Behavioral changes occur in rabies, which usually leads to transmission by biting in infected animals. Subsequently, there is centrifugal (away from the CNS) spread along nerves to multiple organs, including the salivary glands in animals that transmit the virus. Rabies virus is secreted in the saliva in vectors and transmission occurs to other hosts by biting. Bats, raccoons, skunks, and foxes are important rabies vectors in North America, and dogs are the most important vector worldwide. Bat bites may not be recognized and there may even be no known contact with bats.

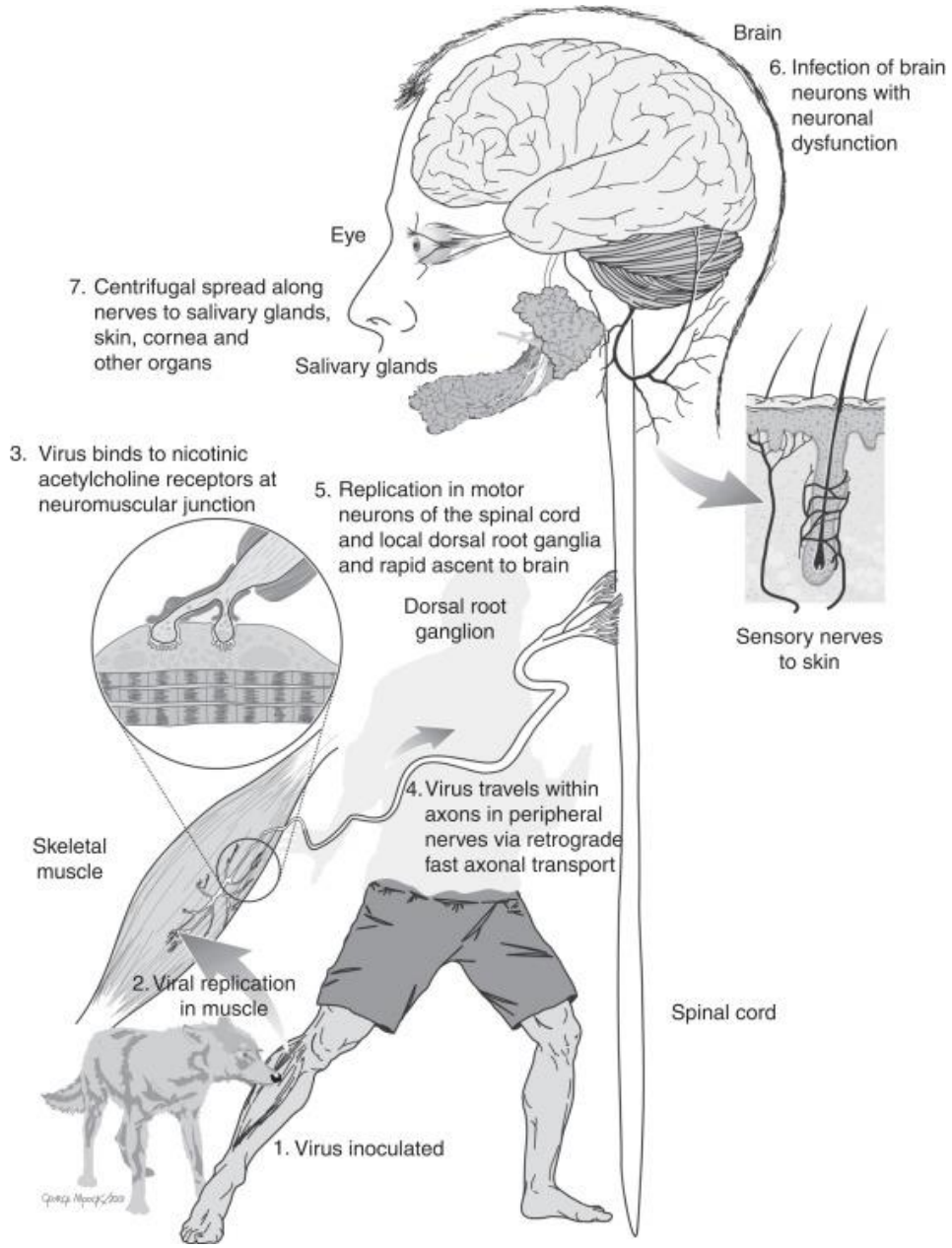


Figure 1: Schematic diagram showing the sequential steps in the pathogenesis of rabies after an animal bite/peripheral inoculation of rabies virus.

Incubation Period For Rabies:

The incubation period is the time between exposure to the virus and the first appearance of symptoms. The period can run anywhere 30 to 90 days on average but may be shorter or longer based on the host and viral factors.

1. **Prodromal Period**

   The prodromal period is described by the first appearance of symptoms. This is when the virus first enters the central nervous system and begins to cause damage.

   The prodromal phase tends to run from two to 10 days on average and may cause such symptoms as:

   - Fever
   - Itching (pruritus)
   - Tingling or burning sensation at the site of the exposure (known as paresthesia)
   - Fatigue
   - Headache
   - Anxiety
   - Irritability
   - Chills
   - Insomnia3
   - A general feeling of unwellness (malaise)
   - Loss of appetite (anorexia)
   - A sore, swollen throat (pharyngitis)

2. **Acute Neurologic Period**

The acute neurologic period lasts anywhere from two to ten days and will almost invariably end in death. The types and characteristics of symptoms can vary, depending largely on how severe or mild the initial exposure was.

Furious rabies is the type most people with experience. As its name suggests, this form of rabies is characterized by violent physical and neurologic symptoms. Symptoms may come and go, and will often be interspersed with moments of calm and lucidity. Death will most often be caused by cardiorespiratory arrest.

Paralytic rabies accounts for about 20% of cases and will cause muscles to gradually weaken, starting from the site of the exposure and expanding outward. Paralysis and death will eventually ensue (usually by respiratory failure).

Atypical rabies is a type most often associated with bat bites. It may involve symptoms from both furious and paralytic forms of the disease. The variations in symptoms and severity can often make it hard to recognize a case as rabies.

Symptoms of rabies occurring during the acute neurologic period may include:

- Agitation
- Hyperactivity
- Hyperventilation
- Excessive salivation
- Hydrophobia (a distressing symptom characterized by an unquenchable thirst, an inability to swallow, and panic when presented with fluids to drink)
- Partial paralysis
- Confusion
- Vomiting blood1
- Aggression (including thrashing and biting)
- Hallucinations
- Seizures6
- Priapism (persistent and painful erection of the penis)3

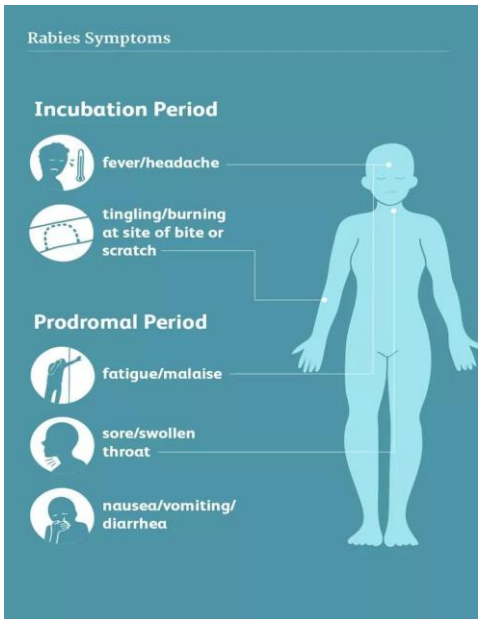
RABIES SYMPTOMS:

Symptoms of human rabies can occur as fast as within the first week of the infection.

The early symptoms of rabies are very generalized and include weakness, fever, and headaches. Without a history of potential exposure to a rabid animal, these symptoms would not raise the suspicion of rabies as they are very similar to the common flu or other viral syndromes.

The disease can then take two forms:

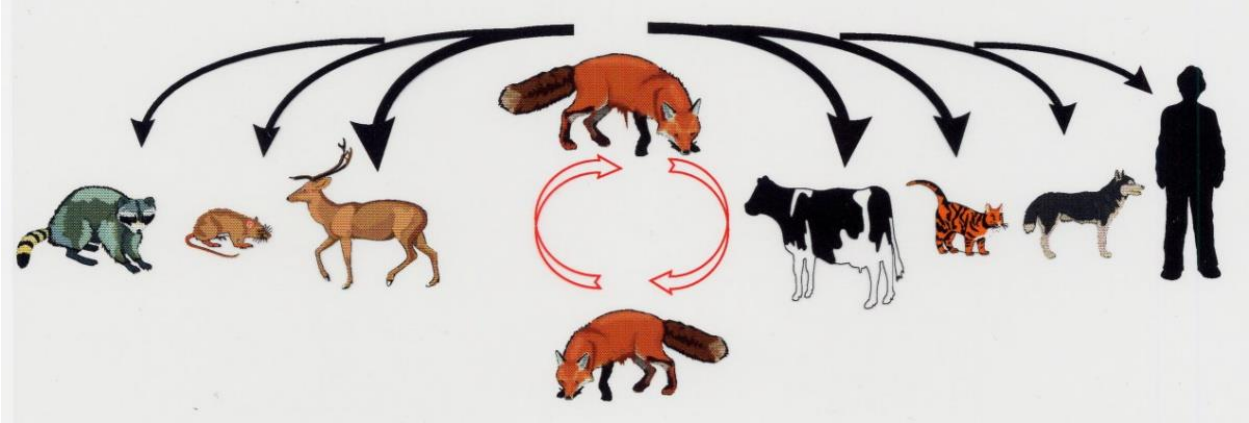
1. With paralytic rabies (approximately 20% of cases), the patient's muscles slowly become paralyzed (usually starting at the site of the bite). This is the less common form and ends in coma and death.
2. With furious rabies (about 80% of cases), the patient exhibits the classic symptoms of rabies, such as:
   - Anxiety and confusion (The patient is often overly active.);
   - Encephalitis, causing hallucinations, confusion, and coma
   - Hypersalaivation
   - Hydrophobia (fear and avoidance of water)
   - Aerophobia (fear of fresh air)
   - Difficulty swallowing.



EPIDEMIOLOGY OF RABIES:

All lyssaviruses have evolved closely with distinct natural reservoir hosts. The latter are animals species in which a pathogen of an infectious disease are maintained independently. For lyssaviruses, these are a wide range of mammalian species within the Carnivora and Chiroptera (bats) orders with a global distribution.

It is generally accepted that bats are the true primary reservoir hosts of almost all lyssaviruses (see bat rabies). However, unlike all other lyssaviruses, rabies viruses (RABVs) as the type species for lyssaviruses have established multiple independent transmission cycles in a broad range of carnivore host reservoirs, where particular RABV lineages circulate within host conspecifics. From the primary reservoir hosts the virus is sporadically transmitted to domestic animals and to humans.



Typical carnivore host reservoirs for RABV are:

- **Africa:** Domestic dog (Canis lupus familiaris), jackals (Canis adustus and C. mesomelas), mongoose (Herpestes spp.)

- **Middle East and Asia:** Domestic dog (Canis lupus familiaris), red fox (Vulpes vulpes), ferret badger (Melogale moschata), golden jackals (Canis aureus)
- **Europe**: Red fox (Vulpes vulpes), raccoon dog (Nyctereutes procyonoides)
- **NorthAmerica:** Raccoon (Procyon lotor), grey fox (Urocyon cinereoargenteus), striped skunk (Mephitis mephitis), coyote (Canis latrans)
- **South America**: Domestic dog (Canis lupus familiaris), crab-eating fox (Cerdocyon thous), marmoset (Callithrix jacchus)

- **Caribbean islands**: Domestic dog (Canis lupus familiaris), small Indian mongoose (Herpestes auropunctatus)

- **Eurasian and American arctic and subarctic regions**: Arctic fox (Alopex lagopus)

Within one geographic region different independent infection cycles may occur simultaneously, as in the Americas where raccoons, skunks, red foxes, grey foxes, coyotes and arctic foxes are primary reservoir hosts.

Zoonotic Virus Human To Human Transmission:

The pandemic potential of zoonotic pathogens lies in their ability to become efficiently transmissible amongst humans. Here, we focus on contact-transmitted pathogens and discuss the factors, at the pathogen, host and environmental levels that promote or hinder their human-to-human transmissibility via the following modes of contact transmission: skin contact, sexual contact, respiratory contact and multiple route contact. Factors common to several modes of transmission were immune evasion, high viral load, low infectious dose, crowding, promiscuity, and co-infections; other factors were specific for a pathogen or mode of contact transmission. The identification of such factors will lead to a better understanding of the requirements for human-to-human spread of pathogens, as well as improving risk assessment of newly emerging pathogens.

DIAGNOSIS AND LABORATORY TESTING:

Several tests are necessary to diagnose rabies ante-mortem (before death) in humans; no single test is sufficient. Tests are performed on samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

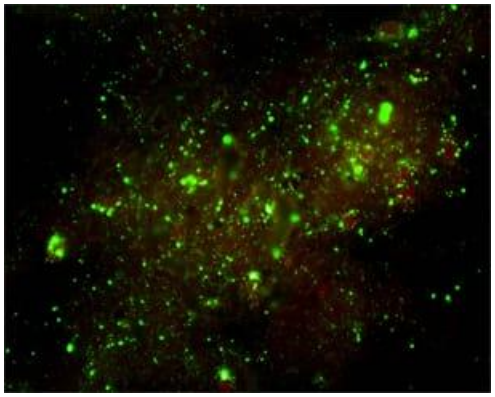
Simple Tests:

- **Saliva test:** You'll spit into a tube. It'll be sent to a lab to look for signs of rabies.
- **Skin biopsy:** Your provider will take a small sample of skin from the back of your neck. Your skin sample will be sent to a lab to look for signs of rabies.
- **Cerebrospinal fluid test (lumbar puncture):** Your provider will use a needle to take a cerebrospinal fluid (CSF) from your lower back. Your CSF sample will be sent to a lab to look for signs of rabies.

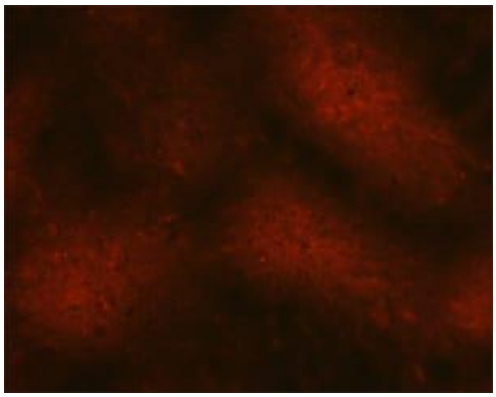
- **Blood tests:** Your provider will use a needle to take blood from your arm. Your blood will be sent to a lab to look for signs of rabies.
- **MRI:** You'll lie in a machine that takes pictures of your brain. Your provider will use the pictures to help determine what's causing your symptoms.

Other Tests:

1. **Direct Fluorescent Antibody Test:**
   The dFA test is based on the observation that animals infected by rabies virus have rabies virus proteins (antigen) present in their tissues. Because rabies is present in nervous tissue (and not blood like many other viruses), the ideal tissue to test for rabies antigen is brain. The most important part of a dFA test is flouresecently-labeled anti-rabies antibody. When labeled antibody is incubated with rabies-suspect brain tissue, it will bind to rabies antigen. Unbound antibody can be washed away and areas where antigen is present can be visualized as fluorescent-apple-green areas using a fluorescence microscope. If rabies virus is absent there will be no staining.



POSITIVE dFA



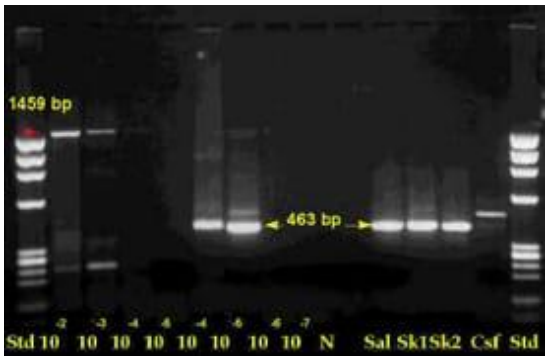
NEGATIVE dFA

Antigen detection by dFA:

The rabies antibody used for the dFA test is primarily directed against the nucleoprotein (antigen) of the virus (see The Virus section on viral structure). Rabies virus replicates in the cytoplasm of cells, and infected

cells may contain large round or oval inclusions containing collections of nucleoprotein (N) or smaller collections of antigen that appear as dust-like fluorescent particles if stained by the dFA procedure.

2. **Amplification Methods:**



PCR TEST RESULT: Indicates positive bands

Samples containing small amounts of rabies virus may be difficult to confirm as rabies-positive by routine methods. Virus isolation in cell cultures increases the virus concentration because the virus replicates in cell cultures. Mouse neuroblastoma cells (MNA) and baby hamster kidney (BHK) cells provide an excellent environment for amplification of rabies virus without the use of animals. Another method for amplifying the nucleic acid portion of rabies virus uses biochemical methods. With this procedure, rabies virus RNA can be enzymatically amplified as DNA copies. Rabies RNA can be copied into a DNA molecule using reverse transcriptase (RT). The DNA copy of rabies can then be amplified using polymerase chain reaction (PCR). This technique can confirm dFA results and can detect rabies virus in saliva and skin biopsy samples.

3. Histologic Examination:

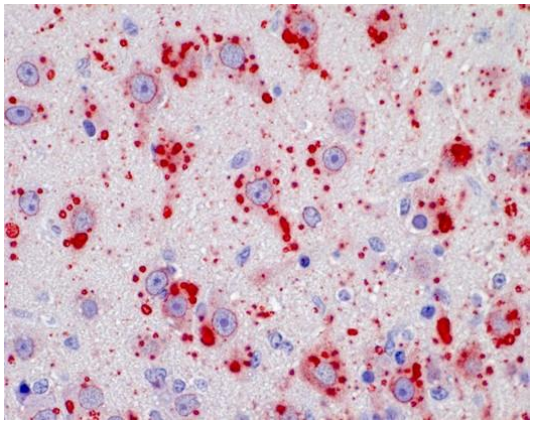
Histologic examination of biopsy or autopsy tissues is occasionally useful in diagnosing unsuspected cases of rabies that have not been tested by routine methods. When brain tissue from rabies virus-infected animals are stained with a histologic stain, such as hematoxylin and eosin, evidence of encephalomyelitis may be recognized by a trained microscopist. This

method is nonspecific and not considered diagnostic for rabies. Before current diagnostic methods were available, rabies diagnosis was made using this method and the clinical case history. In fact, most of the significant histopathologic features (changes in tissue caused by disease) of rabies infection were described in the last quarter of the 19th century. After Louis Pasteur's successful experiments with rabies vaccination, scientists were motivated to identify the pathologic lesions of rabies virus.

Histopathologic evidence of rabies encephalomyelitis (inflammation) in brain tissue and meninges includes the following:

- Mononuclear infiltration
- Perivascular cuffing of lymphocytes or polymorphonuclear cells
- Lymphocytic foci
- Babes nodules consisting of glial cells
- Negri bodies

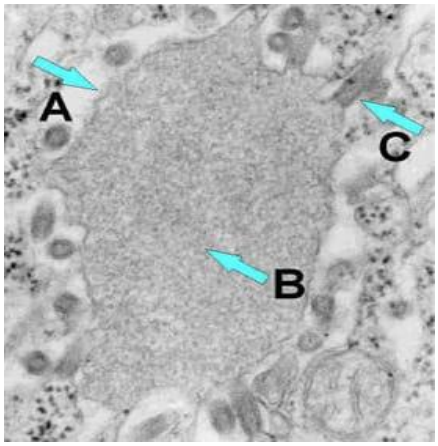
4. **Immunohistochemistry:**
   IHC methods are sensitive and specific for the detection of rabies virus antigen in formalin-fixed tissues. Tissues fixed in formalin must first be processed by routine histologic methods, embedded in paraffin, and sectioned to formalin-fixed paraffin-embedded slides. Rabies virus antigen is detected using specific anti-rabies monoclonal or polyclonal antibodies. IHC testing is more sensitive and specific than histologic staining methods, such as hematoxylin and eosin (H&E) and Sellers stains.



RABIES INFECTED NEURON CELL

5.Electron Microscopy:

The ultrastructure of viruses can be examined by electron microscopy. Using this method, the structural components of viruses and their inclusions can be observed in detail. Rabies virus is in the family of Rhabdoviruses. When viewed with an electron microscope Rhabdoviruses are seen as bullet-shaped particles. A= Negri body,
B= Abundant RNP, C=Budding rabies virus



RABIES VIRUS IN ENDOPLASMIC RETTICULAM

PREVENTION FOR RABIES:

- Vaccinate dogs and cats against rabies as required by law. All dogs and cats more than four months of age must be vaccinated against rabies. Keep vaccinations current at all times.
- Keep dogs and cats under control. Animal control laws prohibit allowing animals to roam unsupervised. Roaming pets are more likely to have been exposed to rabies than those supervised by their owners.
- Leave stray or unknown dogs and cats alone. Loose animals are more likely to have been exposed to rabies and to attack others. Keep pets away from strays, too.
- Leave wild animals alone. Avoid wild animals even if they appear friendly, and do not coax a wild animal to eat from your hand. Do not fear wild animals, just respect and stay away from them. Very young children can learn this rule.

- Do not keep wild animals as pets. Even a raccoon or skunk born in captivity may be a rabies carrier. Local laws prohibit acquiring of keeping such animals as pets. There are no approved vaccines or known quarantine for wild animals.
- Make your property unattractive to wild animals. Cap chimneys and seal off any openings in attics, under porches and in basements. Feed your pets indoors and keep trash cans tightly closed

If you are Bitten, scratched, have contact with animal,

- Immediately wash the wound thoroughly, cleaning and flushing with plenty of soap and water for several minutes.
- Immediately report all animal bites to your animal control agency, police department of health department for follow-up.
- Identify and continue to observe the animal (if wild or stray) to aid its eventual capture, but do not risk exposure again.
- Get prompt medical attention. Call your family doctor or go to the nearest emergency room.

Individual Precautions:

Individuals should follow some safety rules to reduce the chance of contracting rabies.

- *Vaccinate pets:* Find out how often to vaccinate cats, dogs, ferrets, and other domestic or farm animals, and keep the vaccinations up to date.
- *Protect small pets*: Some pets cannot have vaccinations, so their owners must prevent contact with wild animals.
- *Keep pets confined*: Owners should confine pets safely while at home or supervise them.
- *Report strays to local authorities*: Contact local animal control officials or police departments regarding stray animals.
- *Do not approach wild animals*: Animals with rabies are likely to be less cautious than usual and may approach people.

- *Keep bats out of the home*: Seal houses to prevent bats from nesting and call an expert to remove any bats present.

TREATMENT AND FUTURE DIRECTIONS:

If a person has a bite or scratch from an animal that may have rabies, or if the animal licks an open wound, the individual should immediatelyTrusted Source wash any bites and scratches for 15 minutes with soapy water, povidone iodine, or detergent. This might minimize the number of viral particles. They must then seek immediate medical attention. After exposure and before symptoms begin, a series of shots can treat potential rabies infections. Because doctors do not usually know whether the animal had rabies, it is safer to assume that they do and begin vaccination. A small number of people have survived rabies, but most cases are fatal once symptoms develop, and there is no effective treatment at this stage. Instead, healthcare professionals will usually try and make a person with symptoms as comfortable as possible. These individuals may also need breathing assistance.

Rabies vaccine:

Doctors do not offer the rabies vaccine routinely. Instead, they reserve it for those at high risk of rabies exposure, such as laboratory staff working with the virus that causes the disease, veterinarians, and people likely to receive animal bites. These individuals may receive regular vaccinations. Other people may receive the vaccine following exposure to the virus after an animal bite. This is called postexposure prophylaxis. Rabies vaccine contains an inactivated or a harmless version of the rabies virus, so it cannot cause the disease. It triggers the immune response to produce antibodies, which remain in the body and help protect against future rabies infections. Doctors administer the rabies vaccine into the upper arm. Preexposure protection requires three dosesTrusted Source of rabies vaccine across 28 days. For post-exposure protection, previously unvaccinated people need four doses of the rabies vaccine, plus rabies

immune globulin (RIG). Doctors administer RIG as soon as possible, close to the bite wound, to prevent the virus from causing infection in the individual. According to the World Health Organization (WHO)Trusted Source, there are various ways of achieving this depending on the scheduling and frequency of vaccines.

Passive Immunization:

Intradermal active immunization with rabies vaccine at multiple sites is used to accelerate antibody response (the intramuscular route takes at least 1 week to produce immunity). Passive immunization using rabies immunoglobulin (HRIG or ERIG) and monoclonal neutralizing antibodies are employed to achieve viral clearance. Rabies immunoglobulin cannot cross the CNS and can only assist in viral neutralization prior to entry into CNS. Monoclonal rabies viral antibodies (intravenous and intrathecal route) can cross the BBB and, in rat models, immunoglobulins have shown ability to inhibit cell-to-cell spread of virus within the CNS and restrict rabies virus RNA transcription. Postexposure treatment of rats with a monoclonal antibodies successfully resulted in viral clearance from the CNS and protected animals against a lethal rabies virus infection [148]. Ketamine is an anesthetic agent that is considered a potential therapeutic agent in the management of human rabies on account of its inhibitory effect on RNA transcription and N-methyl D-aspartate receptor antagonistic function that might limit viral spreading in tissue [140, 149]. Its ability to rapidly cross the BBB is of potential advantage in reaching the rabies virus within the CNS. Benzodiazepines and barbiturates (γ-aminobutyric acid receptor agonists) have been used for induction of therapeutic coma and to reduce the brain excitatory metabolism and autonomic reactivity. Amantadine and ribavirin have demonstrated antiviral activity [150]. In vitro studies have demonstrated its efficacy [151], but this has not been seen in in vivo studies, owing to its limited capacity to cross the BBB [152]. Intrathecal or intraventricular administration with Ommaya reservoir might be of benefit, but a trial in a

single human rabies case, using the intrathecal and intravenous routes, failed, in combination with IFN-α [153]. Corticosteroids are not recommended for use as in mouse models as the use of corticosteroids increased the mortality rate and shortened the incubation period [154]. Lack of inflammatory response, despite widespread antigen distribution in the brain, makes cerebral edema a rare complication in rabies. Hence, corticosteroids are used only for treatment of adrenocortical insufficiency and are not recommended for rabies therapy. It is also believed that corticosteroids may close the BBB and thereby reduce the passage of therapeutic agents through it [155]. Currently, there is no specific, effective treatment for human rabies. A combination of therapies, as mentioned above, has been used, but none has demonstrated significantly promising results in various clinical trials. In addition to the quest for new, efficacious antiviral agents, novel approaches for treating human rabies should include “neuroprotective” agents, induced generalized or localized therapeutic hypothermia, and a combination of various therapeutic approaches [147].

Indications for Institution of Aggressive Therapy:

Wherever excellent critical care resources are available, an aggressive management approach can be considered on a case-by-case basis. Young, healthy, and immunocompetent individuals; patients who have received rabies vaccination prior to onset of illness; those who develop rabies due to a bat variant; early appearance of rabies-neutralizing antibodies in CSF and serum; and mild neurological illness at the initiation of therapy are regarded as favorable circumstances in which to attempt aggressive therapy [147]. In the early stage of the illness, when results of diagnostic tests for rabies may not yet be positive or unavailable, treatment initiation should not be delayed if there is strong clinical evidence in support of a diagnosis of rabies [137].

Pharmacological Bases for Aggressive Therapy:

Currently aggressive therapy combines the use of antiexcitatory (ketamine) and antiviral drugs (ribavirin, amantadine,) and intensive care, while immune response is enhanced by immunization (active and passive immunization, monoclonal antibodies).

CONCLUSION:

In conclusion, the rabies virus remains a significant global health concern due to its high fatality rate and the challenges associated with prevention and treatment. Rabies is a zoonotic disease primarily transmitted to humans through the bite or scratch of an infected animal, most commonly dogs. Once symptoms develop, the disease is almost always fatal, making prompt medical intervention crucial. Prevention strategies, such as widespread animal vaccination campaigns and responsible pet ownership, play a vital role in controlling the spread of rabies. While effective vaccines exist, access to timely medical care and awareness about the virus are essential in reducing human fatalities. Continued research efforts and public education are necessary to improve our understanding of the virus and develop more accessible and affordable treatments and prevention methods.

ABBREVIATIONS:

- RV- Rabies virus
- CNS- Central nervous system
- PEP- Post-exposure prophylaxis
- WHO- World Health Organization
- CDC- Centers for Disease Control and Prevention
- RIG- Rabies immune globulin
- HDCV- Human diploid cell vaccine
- PVRV- Purified Vero cell rabies vaccine
- RFFIT- Rapid fluorescent focus inhibition test
- ELISA- Enzyme-linked immunosorbent assay

- NHP- Non-human primate
- VNA- Virus neutralizing antibody
- NSP- Nonstructural protein
- ABLV- Australian bat lyssavirus
- EBLV- European bat lyssavirus

CONFLIT OF INTREST:

Nil

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