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Rabies: A review on clinical signs, prevention and control

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Abstract
Rabies is caused by virus belonging to the genus Lyssavirus and family Rhabdoviridae. Rabies is a zoonotic, fatal and progressive neurological infection affecting all warm-blooded animals. Because the rabid animal dies suddenly upon becoming ill, it is an acute disease. The virus is secreted in the saliva of an infected animal and it is spread by all homoeothermic animals. Wildlife such as raccoons, skunks, bats and foxes are the principal rabies reservoirs and are primarily responsible for transmission through bites from rabid animals and saliva of infected hosts. There is a wide range of incubation time, from two weeks to six years (average 2-3 months). Neuropathological lesions are relatively modest, despite significant neurologic symptoms and a deadly end. The rabies virus uses a number of strategies to sidestep the host's immunological defence. As a significant zoonosis, early treatment, as well as successful preventative and control measures, depend on accurate and speedy diagnosis. The gold standard test for determining whether rabies is present in fresh brain tissues is the direct immunofluorescent test (dFAT). Other methods including the polymerase chain reaction and mouse inoculation technique can also be used for diagnosis.

Keywords: Rabies, transmission, clinical signs, diagnosis, prevention and control

Introduction
Rabies is an ancient and prevalent zoonotic disease caused by Lyssavirus belonging to the Rhabdoviridae family (Ayele *et al*., 2018) [3]. It is a well-known viral disease that affects the central nervous systems of all warm-blooded animals, including humans (Moges, 2015) [38]. Prodromal, excitation (furious) and paralytic (dumb) are the three forms that are traditionally used to characterise animals. Because the virus is present in the saliva of infected animals, bites, scratches or licks that cause torn skin or mucous membranes can spread the disease (Jackson, 2010) [25]. It causes fatal encephalitis in mammals. Once the virus's symptoms worsen, the condition is invariably fatal and regrettably, only preventable (Abera *et al*., 2015) [1]. In developing countries, dogs in particular continue to serve as the major reservoir, whereas in developed areas, wildlife species serve as hosts (Rupprecht *et al*., 2008) [43]. Sylvatic rabies poses a rising threat to the human population as well as to domestic animals in many countries and it is spread by wild animals, who act as a large and mostly uncontrollable reservoir of the disease (Mustafa *et al*., 2015) [40]. Rabies is one of the major neglected tropical illnesses. Lack of specialised diagnostic and surveillance methods is the key factor contributing to the persistence of rabies as a zoonotic disease in many underdeveloped nations, especially those in Asia and Africa (Lembo *et al*., 2006) [29].

Etiology: The Rhabdoviridae family member *Lyssavirus* genus is the cause of rabies. It is a single-stranded RNA virus with the shape of a bullet (Moges, 2015) [38]. When exposed to air, sunlight and dried blood with secretions, it quickly becomes inactive (Tojinbara *et al*., 2016) [48]. The virus's RNA genome has five genes in a highly conserved arrangement. Nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and a viral RNA polymerase (L) are all encoded by these genes.

Transmission: All warm-blooded animals can transmit the *Lyassavirus* infection, while the *Lyssavirus* can also proliferate in the cells of cold-blooded animals (Mustafa *et al*., 2015) [40]. This disease is contracted by the virus entering the body through the saliva of an infected animal as a result of bite, wounds, or unwrapped cuts on the fur or mucous membranes (Langley, 2009) [27]. However, the chances of contracting rabies from a bite are more than that of any other route.

Although the virus seldom spreads from one individual to another, a limited number of instances have been linked to transplant surgery (Srinivasan *et al*., 2005) [45]. The virus moves 50 to 100 mm every day toward the CNS along peripheral nerves (via the rapid axonal transport system). This movement is exclusively retrograde, indicating that the sensory and motor neurons are the source of the infection (Mazarakis *et al*., 2001) [33].

Zoonotic importance: The zoonotic disease rabies causes deadly encephalitis in mammals. Among the most-deadly zoonoses, rabies stands out. The typical rabies virus, which is spread by dogs, is responsible for the vast majority (up to 99%) of human fatalities. Anyone who is bitten by a rabid animal or exposed to its saliva is at danger of contracting rabies. Approximately 60,000 individuals every year die from rabies, mainly in Asia and Africa. Children are more likely to contract rabies. Rabies is endemic in India, where 36% of all rabies deaths occur. The true toll of rabies in India is unknown, but according to the information that is currently accessible, it results in 18,000-20,000 fatalities annually (WHO, 2018) [52].

Pathogenesis: The bite of an infected dog, is the most prevalent method of transmission for rabies (90%) (Chhabra and Ichhpujani, 2003; Blanton *et al*., 2009) [16, 10]. Although oral and nasal infections are uncommon, they have been experimentally used to infect mice (Correa-Giron *et al*., 1976) [18], as well as other animals (Bell and Moore, 1971; Amsden and Johnson, 1975) [7, 2]. Viruses typically enter the body through cuts or wounds rather than through healthy skin. The degree of infection, the site of the bite wound and the quantity of virus in the saliva all play a role in rabies virus infection mortality (Warrell and Warrell, 2004; Hemachudha *et al*., 2013) [49, 23]. At the site of bite, virus remain latent for variable time. The incubation period for rabies is normally between two and three months, although it can also range from one week to a year, depending on the location of virus entry and viral load, for example. Bite wounds, particularly those with bleeding, on the hands, neck, face, and head shorten the incubation period because of the reduced length and increased number of neurons. Before attacking the neurological system, the virus has been demonstrated to replicate in muscle fibres (Murphy *et al*., 1973), which would be a crucial amplification stage to produce enough virus to attack peripheral neurons. At the neuromuscular junction, the virus connects to nerve cells via acetylcholine receptors (Lentz *et al*., 1982) [30]. As soon as the virus infects peripheral neurons, it moves down the motor and sensory axons in the direction of the Central Nervous System (CNS). Virus moves swiftly retrogradely along the course of peripheral nerves (Mazarakis *et al*., 2001) [33]. It has been estimated that virus travels towards CNS within motor and sensory axons with a speed of 12-100 mm/day (Kelly and Strick, 2000) [26]. Widespread dissemination is caused by repeated cycles of axoplasmic transmission, replication, and transneural spread in the perikarya and dendrites. Several cell types of the nervous system have been shown to harbour the virus but infection of glial cells is reported to be relatively uncommon (Jackson, 2000) [24]. The hippocampus, brain stem, and cerebral cortex are particularly vulnerable to rabies infection. The body's other tissues are affected by centrifugal spread via nerves. Rabies virus can spread from CNS to salivary glands, cornea and tonsils.

Clinical signs: The incubation period of this disease ranges form days to months (often for 60 days) and these animals can only get rid of the virus through salivation a few days before the end of the incubation period, often 2 or 5 days before symptoms appear and may last until death. Incubation period also depends on the site of bite (Tepsumethanon *et al*., 2003) [47]. It has been found that an animal's behaviour changes as the disease progresses. The confirmation report of a laboratory test must be used to support any confirmed suspicion of rabies (Chernet and Nejash, 2016) [15]. Clinical abnormalities may be described by variations in tropism at the inoculation site or in the CNS, in the dissemination pathway, or in the triggering of the immunological cascade in the brainstem (Hemachudha *et al*., 2002) [22]. The main clinical symptoms are typically non-specific and include excessive salivation as well as anxiety, restlessness, anorexia or an improved appetite, nausea, diarrhoea, a mild fever, dilated pupils and nausea (Banyard *et al*., 2013) [5]. The clinical signs are categorized into following categories:

Prodromal Stage: After a definite incubation period, clinical signs start to manifest. Small behavioural changes, such as anger in domestic animals, daylight tricks in nocturnal animals, no fear of humans in wild animals, or irregularities in eating, may happen during this first stage, which usually lasts between one and three days (WHO, 2013) [50].

Excitement/Furious stage: Animal becomes aggressive. Agitation, wandering, and yelling are characteristics of the furious type. Crying, polypnea, drooling, and attack on people, other animals or inanimate objects. Animals with the disease frequently consume foreign objects, such firewood and gravel (Bano *et al*., 2017) [4]. The wild animals frequently lose their fear of people, and they may attack people or another nearby animal. On the other hand, nocturnal animals could be visible all day long. Unusual alertness in cattle may be a sign of this stage (Banyard *et al*., 2013) [5].

Dumb/Paralytic stage: The gradual paralysis is the characteristic of the "dumb" form of rabies. There is paralysis of the masseter and neck muscles due to which the animal is unable to swallow and it may salivate excessively (WHO, 2013) [50]. A change in vocalisation, such as an unnatural bellow in cattle or a hoarse howl in dogs, can occur due to laryngeal paralysis. Additionally, the lower jaw may drop or there may be facial paralysis. Ruminants may become dispersed from the herd and develop inert or depressed infections, both *in vitro* and *in vivo*. Rumination might stop (Yang *et al*., 2012) [54]. Additionally observed are ataxia, coordination issues and ascending spinal paresis or paralysis. The difficulty to swallow during this stage results in the classic appearance of foamy saliva around the mouth (hydrophobia). Some animals may start to have paralysis in their hind legs. Eventually, death follows total paralysis (Barecha *et al*., 2017) [6].

Hydrophobia: The phrase, which means "the fear of water", has historically been used to refer to rabies (Smallman-Raynor *et al*., 2004). This condition is a group of warning signals that appear when an infection is progressed and the patients have difficulty swallowing and drinking. Any mammal with a viral infection might exhibit hydrophobia. In this condition, the animal struggles to drink, produces

excessive amounts of saliva, and may experience painful vocal cord and throat muscle spasms. Due to a rabid animal's bite, the virus persists in saliva and is disseminated (Mustafa *et al*., 2015) [40].

Pathology: In rabies infection, spinal cord, peripheral nerves and brain show ganglion cell degeneration as well as perivascular infiltration of mononuclear cells and neuronophagia. An early "axotomy reaction" to infection in gangliocytes is followed by a large number of autophagic compartments. Gangliocytes with advanced stages of degeneration have empty, partially membrane-bound vacuoles (Rossiter *et al*., 2009) [42]. Spinal cord mostly affected in paralytic form of rabies. In the brainstem, hypothalamus, and limbic system, vascular abnormalities such thrombosis and haemorrhages are seen.

Diagnosis: Only after the beginning of symptoms this disease can be diagnosed (WHO). Either in vivo testing or autopsy are used to diagnose rabies. Ante-mortem testing is difficult to use to identify the lyssavirus infection (Chernet and Nejash, 2016) [15]. Despite the fact that hydrophobia is very suggestive, this disease does not have any pathognomonic medical symptoms of infection. Since certain alternative, lab-based tests have been developed for infection confirmation, the historical reliance on the discovery of accumulating Negri-bodies is no longer thought to be appropriate in support of the diagnostic evaluation (Abera *et al*., 2015) [1].

Diagnosis based on clinical signs and history: The neurological symptoms generated by other neurotropic etiological agents often mistaken for the clinical indications of rabies. Incubation times for rabies infection in people and animals can range from 20 to 90 days on average. Early symptoms (2-5 days in duration) escalate in 75% of dogs to paralytic or dumb versions (Hemachudha *et al*., 2013) [23]. Four to eight days after the onset of clinical symptoms, paralysis and mortality occur in both clinical types. A preliminary diagnosis can be obtained using some typical clinical signs seen in dogs and other animal species (Blanton *et al*., 2010) [9]. For ten days, the animals exhibiting anomalous behaviour should be segregated and prohibited from biting others. The prodromal phase of rabies is characterised by noticeable behavioural abnormalities. They can be irritable, more sensitive to noise and light, alert, friendly and aggressive (more so in cats) and attack without warning, or they can become despondent and hide in dark areas, exhibit a minor pyrexia, have a compromised corneal reflex, and self-mutilate at the bite site. Both the encephalitic (furious) and paralytic (dumb) clinical forms of human rabies involve the brainstem (Hemachudha *et al*., 2002) [22]. At the site of the bite wound, itchiness, discomfort, or parasthesia are some of the prodromal signs of rabies. In contrast, furious rabies is characterised by irritability, agitation, hyperaesthesia, autonomic disturbances, and hydrophobia, which is a pathognomonic symptom caused by a triad of inspiratory muscle spasm, painful laryngospasm (Meslin, 2005) [36].

Clinical samples: The antemortem diagnosis is performed on clinical samples, including CSF, saliva, swabs from the nasal mucosa, eye and throat, impression smears from the eyeball and cornea, biopsies from the skin on the face and nuchal regions and brain tissues (brainstem, cerebellum and hippocampus) are taken in case of dead animals (Warrell and Warrell, 2004) [49]. Skin biopsies can be used to diagnose rabies in both humans (Blenden *et al*., 1986) [12] and animals (Blenden *et al*., 1983) [11] both before and after death.

Isolation of virus: The most accurate ways to diagnose rabies are by isolating Lyssa virus. Isolation can be done from 2 days old newborn albino mice, 3 to 4 week old mice, or cell lines (such as the mouse neuroblastoma cell line Neuro2a/CCL 131, the baby hamster kidney (BHK) 21/C13, the American type culture collection (ATCC), Vero cell, and McCoy cell) (Singh *et al*. 2017) [44]. Following infection with fixed and street RABV, the McCoy cells displayed a cytopathic effect within 24-72 hours. Based on the cytopathic effect (CPE), increased viral generation, and high interferon (IFN) sensitivity, they function as a valuable tool (Frana *et al*., 2008) [21].

Virus and virus antigen detection: Light microscopy can be used to demonstrate Negri bodies as acidophilic, oval or spherical, and highly reflective to haematoxylin-eosin staining, magenta coloured Negri bodies with small (0.2-0.5 mm) and dark blue inner basophilic granules by Seller's staining, and red colour to Mann's staining. As a result of their extremely poor sensitivity, techniques used in histological sections like Seller's stain can no longer be advised. Viral inclusions and virus particles can be found using electron microscopy (Singh *et al*., 2017) [44]. The immunoperoxidase technique (IPT), enzyme immunoassay and immunofluorescence are used for the direct detection of rabies virus antigen (Mani and Madhusudana, 2013) [32]. Animal rabies can be diagnosed using a variety of techniques, including direct fluorescent antibody, mouse inoculation, tissue culture infection and polymerase chain reaction. WHO has recommended all of these methods (Bourhy *et al*., 2005) [14] (Table 1).

All laboratories involved in rabies diagnosis routinely use the direct immunofluorescent test (dFAT). OIE and WHO both suggest the dFAT as the most common rabies diagnostic test (OIE, 2009; WHO, 2013) [41, 50]. The dFAT is 100% sensitive to fresh brain material, and a confirmatory diagnosis can be made in within two hours. However, this method is time-consuming and poses a significant risk of virus exposure to the lab diagnostician. Additionally, this method is inappropriate since it has lesser sensitivity when the brain samples autolyze at warm temperatures (David, 2012; McElhinney *et al*., 2014) [19, 34]. The brainstem showed the highest FAT sensitivity of 99.6%, followed by the cerebellum (99.3%), cerebrum (98.9%) and hippocampus (98.7%) (Tepsumethanon *et al*., 1997) [46]. Immunoperoxidase techniques can be used as an alternative of FAT since they are similarly sensitive, but necessary precautions must be taken to prevent non-specific, false-positive results. Its benefit is the use of peroxidase conjugate on freshly isolated nerve tissue or formalin-fixed tissue sections for immunohistochemistry testing (Lembo *et al*., 2006) [29].

Viral nucleic acid detection: In situ hybridization, PCR, genomic sequencing and other nucleic acid (NA) based procedures have been developed and are used in WHO or OIE reference laboratories for rabies diagnosis (Meng *et al*., 2013) [35]. The most sensitive method of molecular detection is

polymerase chain reaction (PCR) and nucleic acid sequence-based amplification, however both methods have the potential to give false-positive or false-negative results and should only be used in conjunction with other established methods (Bordignon *et al*., 2005) [13].

Table 1: Diagnostic techniques for Rabies

Techniques	Samples	Advantages/disadvantages
Mouse inoculation test	Pancreas, liver, brain, spleen, and salivary gland	Only freshly collected samples give good results
Direct Fluorescent anti body test (dFAT)	Pancreas, liver, brain, spleen and salivary gland	Most tissue sources are acceptable, although decayed tissue is excluded
Polymerase chain reaction	Cerebrospinal fluid, bodily fluids, saliva, and urine	Application in all tissue conditions, although a skilled technician is needed.

Prevention and Control

The management of animals is now the cornerstone of rabies prevention and control (Larghi, 2004; Cleaveland *et al*., 2006; Fooks, 2007; Leung *et al*., 2007; Wilkins and Piero, 2007; Rupprecht *et al*., 2008; Blancou, 2008) [28, 17, 20, 31, 51, 43, 8]. Animal rabies control mostly consists of vaccinations for dogs and cats, the eradication of stray animals, public health awareness campaigns, etc.

Pre-exposure vaccination: Pre-exposure prophylaxis is a type of rabies vaccination that is given to prevent from contracting the disease in humans before coming into contact with a rabid animal or any other potential source of rabies virus exposure. Pre-exposure vaccination is advisable to people at high risk of exposure like veterinarians, laboratory staff working with rabies virus, veterinary technicians, animal control officers, wildlife rehabilitators, zoo employees, wildlife handlers/officers, animal handlers, children living in areas at risk and individuals living in or travelling to areas of risk. Immunization protocol includes injections at 0, 7 and 28 days. For animal use, rabies vaccines consist of live attenuated virus, inactivated and recombinant vaccines. Although rabies vaccines are often lyophilized, they can also be stored in liquid form after being inactivated with an adjuvant.

Post-exposure vaccination and management: Post-exposure vaccination of rabies is carried out after the bite of rabies suspected animal to prevent the development of disease (Table 2). The post-exposure vaccination schedule consists of 5 doses of intramuscular injection of cell culture vaccines on days 0, 3, 7, 14 and 28 for post-exposure prophylaxis (Singh *et al*., 2017) [44]. There are restrictions on using injectable vaccination preparations, particularly in carnivores and wildlife. Therefore, efforts to construct an oral vaccine have been ongoing with positive outcomes. As per WHO and OIE, use of oral rabies vaccination (ORV) should be encouraged in free-roaming dogs to control dog-transmitted rabies (Yale *et al*., 2022) [53]. Modified live vaccine and vector-based vaccine are two types of ORV currently in use. When dogs cannot be easily held or captured for parenteral vaccination, it has been demonstrated that oral rabies immunisation of dogs improves the coverage of mass vaccination campaigns. The WHO, OIE, and other international experts' consistent and growing endorsement for the use of modern ORVs in pilot field activities gives national authorities confidence in their evaluation of the suitability of these devices (Yale *et al*., 2022) [53].

Table 2: Type of contact, extent of exposure and suggested post-exposure treatment

Category	Type of Contact	Type of Exposure	Recommended Post Exposure Prophylaxis
I	Touching or feeding of animal licks on intact skin	None	None, if reliable case history is available
II	Minor scratches or abrasions without bleeding	Minor	Wound management Anti-rabies vaccine
III	Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva	Severe	Wound management Rabies immunoglobulin Anti-rabies vaccine

Any animal exposed to a proven or possibly rabid animal must be placed under rigorous quarantine for a period of six months. The following actions make up a swift and thorough reaction for the disease's effective control and elimination:

- The source of the virus's invasion must be identified and controlled.
- Viral characterization at a local reference lab, a national lab, and an international level.
- Increased rate of rabies immunisation in animals.
- Mobility restrictions on animals.
- Provision for public outreach and professional education.

Conclusions

The rabies virus is a lethal disease that can affect both unvaccinated animals and humans. Both farmed animals and pets can be vaccinated against the lyssavirus, which will help control the disease. Because prevention is preferable to treatment, rabies can be prevented by avoiding direct contact with rabid animals, their mucous membranes, and wounds as well as by providing wildlife workers, veterinarians, animal handlers and laboratory personnel with the necessary training.

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