A Mad Dog Disorder: Rabies and its Epidemiology, Prevention and Control

Shamreza Aziz[1,*], Ayah Talal Zaidalkilani[2], Ammar AL-Farga[3], Shahid Hussain Farooqi[4] and Tayyaba Ameer[5]

[1]Department of Epidemiology & Public Health, University of Veterinary & Animal Sciences, Lahore, Pakistan
[2]Faculty of Pharmacy and Medical Sciences, Department of Nutrition, University of Petra, Amman, Jordan
[3]Department of Biological Sciences, College of Science, University of Jeddah, Jeddah, Saudi Arabia
[4]Department of Clinical Sciences, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS-Lahore, Pakistan
[5]Department of Farming Managment, Weihenstephan-Triesdorf, University of Applied Sciences, Triesdorf, Germany
*Corresponding author: shamrezaaziz@gmail.com

Abstract

Rabies is a fatal neurological disorder which is caused by rabies virus which belongs to the genus Lyssavirus of family *Rhabdoviridae*. The virus majorly affects all warm-blooded animals and causes disease in them. The prevalence of disease is high in many developing countries and it prevails as an endemic disease in many countries while some countries and islands have been free from the rabies but the threat of reemergence still present. Rabies affects a large number of individuals with a high mortality rate and an estimated 60,000 people die every year due to this disease. The main source of transmission of the virus is through the bite of rabid animals or through saliva of infected individuals. The wildlife and bats are the major natural reservoir of the virus. The incubation period of the rabies virus is highly variable but generally ranges from two to three months but it may last up to years. Rabies virus shows different mechanisms to evade the immune responses of the host. For early detection and treatment of the disease, rapid diagnostic methods are necessary. Direct fluorescent antibody test is a standard test for the diagnosis of rabies virus. However, polymerase chain reaction is also used as a superior test for regular diagnosis. Different antivirals have been used to treat the infection, immunoglobulin and vaccines are also used to treat and control the virus. This chapter aims to explore detail about transmission, mode of action, diagnosis, treatment, and prevention strategies for the control of rabies virus.

Keywords: Rabies, Dog bite, Developing countries, Direct fluorescent antibody test, Treatment, Vaccines, Control

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Introduction

The word rabies comes from 'rabere' which is a Latin word. Rabere means "mad" so the rabies refers to a disease which causes madness. From the beginning of human civilization, this disease has been recognized (Tarantola, 2017). Since prehistoric times, the relationship of rabies and its association with dog bites have been known to humans (Gorman, 2002). Rabies is known as both emerging and re-emerging disease as it is emerging in those areas where it was not present before while in areas where it was present but eradicated, the disease is known as re-emerging (Rupprecht et al., 2020). The mortality rate per year of rabies has been calculated as nearly 59000 in the human population. The most vulnerable population include both socially and economically disadvantaged groups of the society (Regea, 2017; Barbosa Costa et al., 2018; Tiwari et al., 2019). The main target of the rabies virus is the nervous system of the mammalian host. Morphologically the rabies virus is a negative sense, unsegmented, neurotropic, single-stranded RNA virus (Samad et al., 2024). The primary route of transmission and maintenance of the virus is due to the bites of free roaming or stray dogs (Rahman & Isloor, 2018). The disease is widespread in nations that do not have any legislation regarding the ownership of dogs and their movement, the rules either not present or not strictly followed (Özen et al., 2016; Taylor et al., 2017). The prime source of human rabies infection is the domestic dog while other wild carnivores and bats serve as the natural reservoir of the virus (WHO, 2018a). Rabies is present all over the world in many countries with the exception of some isolated islands and countries. In these exceptional countries and islands the virus either has been eradicated or it has never been reported (WHO, 2018b). However, these countries are still at a risk of emerging or re-emerging of the virus and the source may be the infected animals or wildlife reservoirs causing a spillover event (Castrodale et al., 2008). It has been reported that there are deaths of patients from rabies in countries which are rabies free and the reason recorded is the exposure of the patients to the virus when they were visiting the endemic countries (Meslin, 2005). The disease is endemic in developing countries in Asia and Africa while some countries are most affected with rabies, the disease is also endemic in some nations of South America (Ortiz-Prado et al., 2016). The World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization of Animal Health (OIE) supported a program named Global Action Plan (GAP) to eliminate rabies. Working in collaboration, the purpose of these three organizations is to eliminate rabies from the world by 2030 (Rupprecht et al., 2020).

Epidemiology and Transmission of Rabies Virus

All endotherms are more prone to lyssavirus disease; additionally, cold-blooded animals can also acquire lyssavirus infection (Mustafa et al., 2015). The spread of rabies virus happens by direct contact of virus with bite wounds, open skin wounds, or mucous membranes when exposed to saliva of infected animal, nerve tissue, airborne transmission, or organ transplantation with infected tissues (Wyatt, 2007; Fitzpatrick et al., 2012). As they have very close relation to humans, dogs are approximately fifty times more likely to snap someone than slurring or scratch them, which only happens between 0.1% and 1% of the time (Tang et al., 2005; Aghahowa & Ogbevoen, 2010). The reason for 85%-95% of rabies cases is its transmission by snaps. The virulence of the disease, location of the wound bite, and amount of virus in the saliva will affect the mortality of the illness. The incubation period for rabies is usually two to three months but may vary from one week to a year. In general, 54% of cases may last from one to three months, 30% could last 30 days, and 15% for about three months. The incubation period for the rest 1% of the infections may last longer than a year. In extremely unique cases, it may even stretch up to 25 years depending on the viral load, the virulence of the strain, the severity, and the area of the bite (Johnson et al., 2008; Shankar et al., 2012; Hemachudha et al., 2013; Baer, 2017). In rare instances, viruses can enter the body through non-bite exposures such as aerosols, organ and cornea transplantation, infection of open wounds with saliva, mucosal membranes, or contaminated substances (Javadi et al., 1996; Charlton et al., 1997; Gibbons, 2002; Hellenbrand et al., 2005; Krebs et al., 2005). Proper system should be taken for pre-and post-exposure prophylaxis. Rabies virus specifically lives in the intra-neuronal state whilst in the incubation stage. Anyhow, it is still not known if healthy blood givers might shift the disease to the recipient whilst the incubation period. So, it is prohibited to give organs and hematology for a year after post-exposure prophylaxis against the rabies virus (Figure 1).

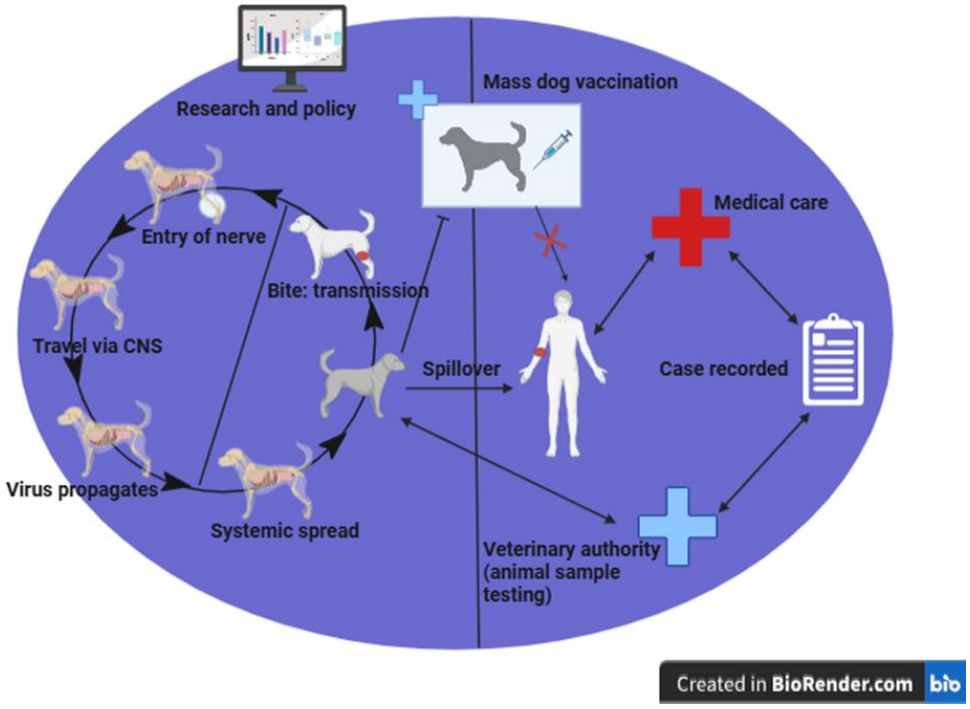

Fig. 1: The cycle of transmission of rabies and highlighting the need of interventions (medical and veterinary) to control deaths in the human population.

Mode of Action

As the infection starts, the rabies virus replicates at low levels in the muscle cells of its host. This starting phase of viral replication is known as smouldering infection and it may last for weeks. This phase may also last for as long as a year and the reason behind is the presence of a host specific microRNA 133 present in the muscle cells. This RNA of the host's muscle cells interrupted the process of transcription and translation of the rabies virus (Charlton et al., 1997; Israsena et al., 2011). The phase of smouldering infection is not or less visible to the immune system of the host which results in the reduction in the innate immune response by the host towards the rabies virus (Lafon, 2004). Additionally, it is believed that the underlying mechanisms of immune alteration by the virus may upregulate the immunosuppressive genes which in turn limit the ability of host immune system to recognize the pathogen (virus) which ultimately resulted into the impaired response of type 1 interferon again the rabies virus (Baloul et al., 2004; Lafon et al., 2008). Furthermore, viruses also suppress the antiviral response of the host through viral phosphoprotein P. This phosphoprotein P works by antagonizing the interferon signalling of the host immune response through the signalling pathway of phosphorylated signal transducer and activator of transcription proteins (STAT), inhibiting STAT nuclear localisation (Brzózka et al., 2006; Ito et al., 2010; Wiltzer et al., 2014). If the virus replication fails at the early stages, the virus gets access to the central nervous system (CNS) of the host. This is done when the viral glycoprotein G binds to different types of receptors present on the motor endplate of the neuromuscular junction which results in the stimulating of the process of receptor mediated endocytosis (Lafon, 2005; Wang et al., 2018). After that the virus is transported through a microtubule transporter along the motor axon in a retrograde fashion and reaches the first order motor neuron which is directly associated with the muscle where the host gets bitten. The longer period of incubation of the rabies virus is attributed to the fact that the virus cannot travel through sensory or autonomic nerves especially in case of superficial bites (Hemachudha et al., 2013). There are many factors associated with the failure of viral eradication at the CNS. The phase of smouldering

infection is responsible for poor adaptive immunity response which result in late activation of lymphocytes and their migration through the blood brain barrier, and on the other hand viruses also cause destruction of lymphocytes (Hooper et al., 2009; Hooper et al., 2011). The neuron cells which are now infected with rabies virus promote autophagy to apoptosis, a process of self-destruction as a response to stress and also work to inhibit spread of pathogens intracellularly (Peng et al., 2016). The process of autophagy is more controlled and it serves to preserve the structure of CNS as compared to apoptosis. Due to the presence of phosphoprotein P in rabies virus the process of autophagy is not complete in the virus. This results in neuronal survival but it also favors the virus to continue replication and become viable (Nikolic et al., 2016; Liu et al., 2017). After 48 hours of propagation of virus in CNS, virus starts spreading slowly in an anterograde pattern from the spinal cord to other organs through their respective autonomic and sensory neurons for instance salivary glands (Hemachudha et al., 2013). After four days, the CNS becomes highly infected with the virus (Figure 2).

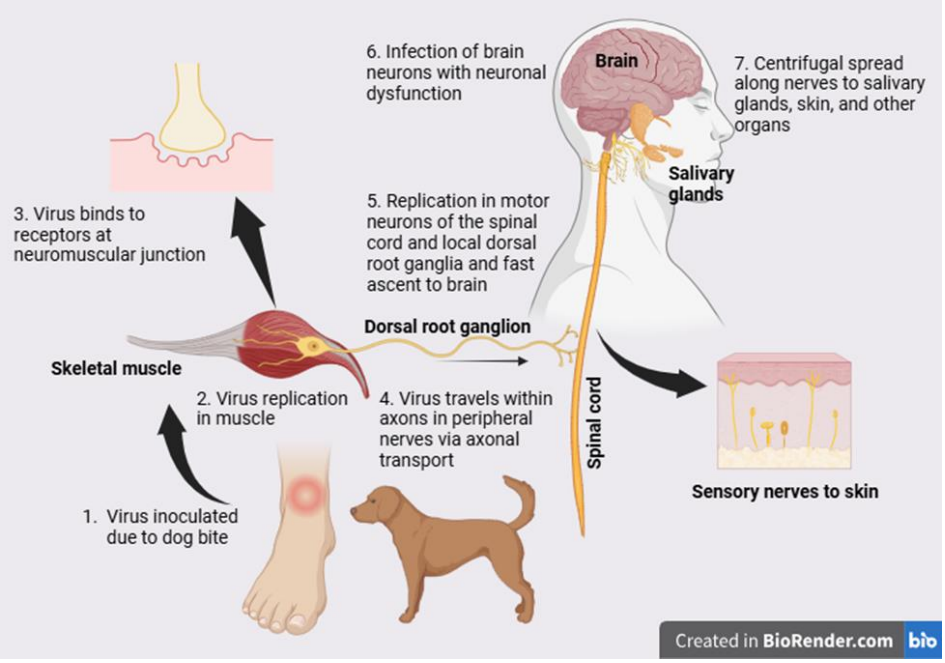

Fig. 2: The mechanism of action of rabies virus.

Clinical Manifestation of Rabies Virus

Rabies are divided into two different forms the first one called furious rabies and the other is called paralytic form. The case ratio for furious and paralytic rabies is 3:1 respectively. The mechanism of action of the two forms which mainly differentiate between the two forms is still under discussion (Bintang et al., 2023). The postmortem examination of both forms of rabies has no differences both in the distribution of viral antigens and the degree of inflammation caused by the infection. The electrophysiological examination of the furious form of rabies shows impairment and dysfunction of the cells of the anterior horn of spinal cord. In postmortem examination, central chromatolysis can be identified. However, peripheral nerve dysfunction, myelinopathy, or axonopathy can be assessed in the case of the paralytic form of rabies which play a significant role in the onset of paralysis (Shuangshoti et al., 2013).

Diagnostic Methods

Laboratory tests apply on the samples of rabies only when the manifestations of the disease appear because there are no tests available yet that can identify the pathogen of rabies during the entry of the pathogen and before the appearance of the first symptom of the disease. If there is a death of any human or animal and a medical doctor or vet suspects rabies based on history or symptoms the gold standard method for confirmation of rabies is a direct fluorescent antibody test (FAT) (Rupprecht et al., 2018; WHO, 2018c). In this technique, brain tissue samples are collected and observed under a special kind of microscope called a fluorescence microscope which shows bright fluorescent light if samples are positive. Rabies virus has a nucleoprotein antigen which is present in positive samples. The brain tissue samples are incubated with special kinds of antibodies which are only made for rabies virus. These antibodies are labeled with fluorescein isothiocyanate. If a virus is present in samples these antibodies will attach to antigens of rabies. When we examine an impression smear under a fluorescence microscope, if rabies antigens are present it will show fluorescence otherwise not. This technique can also be used before death for the detection of the rabies virus. For this corneal samples from the eyes or nuchal skin which is the back of neck tissue are collected. However, there is a limitation of this technique because it might show more false positives and more false negatives in corneal and nuchal skin samples. Also, there is a risk of damaging the cornea during sampling which may lead to blindness. Therefore, sampling from the cornea is not recommended (Lembo et al., 2006).

We can also identify rabies virus infection histopathologically by using eosin dye. In this method, brain tissue samples are collected and preserved in a formalin solution. Then samples are examined after treatment with dyes. There are special intracytoplasmic inclusion bodies in the positive samples of rabies. These are 'Negri bodies' which are diagnostic hallmarks of rabies infection. However, there is a limitation of this test because it can show negative results for those who may still have had rabies. Therefore, it is not used as a single primary test (Ashwini et al., 2024). If the results are negative fluorescent antibody tests should be considered.

We can also identify rabies infection by rabid immunochromatographic diagnostic tests or lateral flow assays based on immunochromatography by collecting brain samples after death or saliva samples of live suspects. These techniques can be used for early diagnosis of diseases where rabies cases are common. It means that we can apply them in field conditions outside of the lab. As rabies is a fatal disease we can apply these techniques on a large scale where there is a risk of rabies and taking into account the results we can consider confirmatory diagnostic tests such as fluorescent antibody tests (Eggerbauer et al., 2016; Léchenne et al., 2016; Servat et al., 2019; Yale et al., 2019; Klein et al., 2020; Tenzin et al., 2020).

The indirect fluorescent antibody test is a quick test that detects IgM antibodies during the early stages of infection and IgG antibodies during the later stages of rabies infection. However, there is a limitation of this test as it has cross-reactivity with other viruses which can cause brain infections (Rudd et al., 2013). So when there are positive results it might be an infection other than rabies virus. ELISA is a test that can identify rabies virus infection in which antibodies attach with viral nucleoprotein or glycoprotein. It is most widely used in laboratories with basic facilities for the detection of rabies infection (Feyssaguet et al., 2007; Welch et al., 2009; Realegeno et al., 2018).

Conventional or real-time reverse transcriptase PCR, nucleic acid sequence-based amplification,loop-mediated isothermal amplification, and microarray-based assays are the techniques that are used for detecting rabies genetic material such as DNA and RNA (Wacharapluesadee & Hemachudha, 2010; Muleya et al., 2012; Zandi et al., 2022). The most commonly used techniques for confirming rabies virus in the samples which are collected from dead or live humans or animals are conventional or real-time reverse transcriptase PCR. There are specialized guidelines that are followed during the detection of rabies genetic material in these techniques which specifically target the rabies nucleoprotein (N) gene or other parts of rabies genetic material (Wakeley et al., 2005; Wacharapluesadee et al., 2008; Nadin-Davis et al., 2009; Wadhwa et al., 2017).

Treatment and Preventive Measures

After the exposure to the virus most probably due to bite, the wound site should be washed with soap immediately and immunized. The directions for the patient include silence, in dark areas and appropriate supply of oxygen and nutrition. Specific therapy includes active immunization that is use of rabies vaccine, passive immunization that is use of immunoglobulin, antivirals such as ribavirin, amantadine, interferon-α, and ketamine HCL. Avoid the use of minocycline and corticosteroids as these may worsen the condition (El-Sayed, 2018). To hinder the replication process of viruses, immunotherapy and antiviral therapy are considered of great importance. In vitro antiviral therapy has promising outcomes while in vivo antiviral therapy has less clinical importance yet. Immunotherapy has significant results against rabies when used as a monoclonal antibody as it targets rabies viral protein (Knobel et al., 2022). For the post-exposure prophylaxis, monoclonal antibodies have been developed as an alternative for anti-rabies immunoglobulin since 1990. More research needed regarding the dose calculation of the monoclonal antibodies used as passive immunization against rabies. Monoclonal antibodies have significant positive results to be used as prophylaxis against rabies. Milwaukee Protocol also has been used to treat symptomatic rabies but still it has not produced significant conclusive outcomes. In this protocol, coma is introduced in the patient using ketamine and amantadine. The two monoclonal antibodies including RVC20 and RVC58 have been thought to be developed as a significant treatment regime against rabies in humans. In trails, these two monoclonal antibodies show therapeutic effects towards symptomatic rabies in mice (de Melo et al., 2020; de Melo et al., 2022). There are several types of vaccines used against rabies, for instance cell cultured or embryonated egg-based vaccines (CCEEVs), purified Vero cell rabies vaccine (PVRV), and human diploid cell vaccine (HDCV). PVRV has been largely used in developing countries according to WHO recommendations, injected intramuscularly or intra-dermally. The two regimens recommended by WHO include Essen regimens and Zagreb regimen. In the Essen regimen, five doses are injected (1-1-1-1-1) on days (0, 3, 7, 14, 28). In the Zagreb regimen, five doses were injected (2-0-1-0-1) on days 0, 7, and 21 (Ahmad et al., 2022).

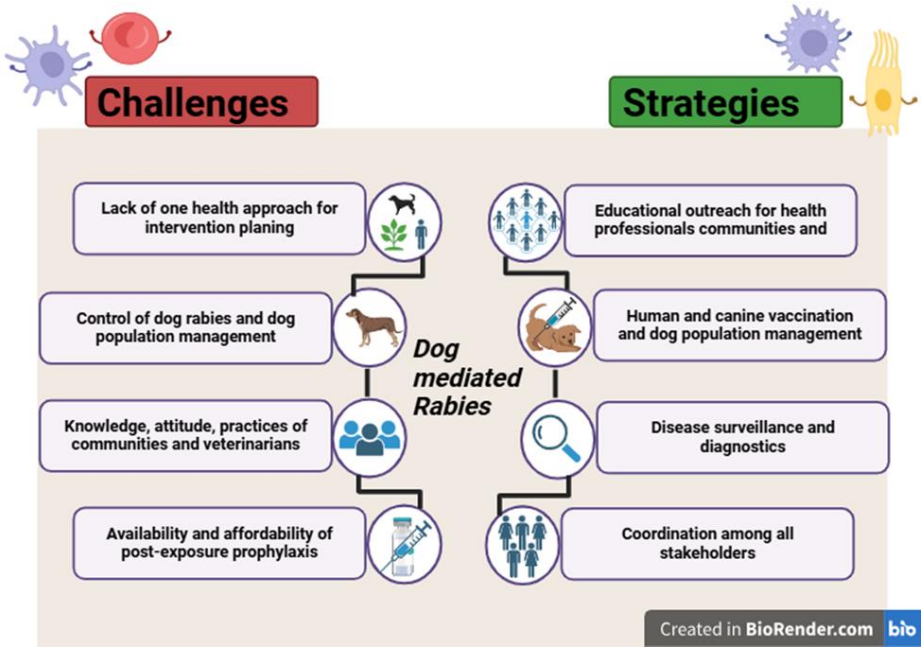

Fig. 3: Overview of challenges and strategies to control rabies.

Control

Rabies is still widespread and least understood especially in underdeveloped or developing countries, because human healthcare is not 'enough and canines at house level have not been widely vaccinated. Despite rabies also transfer by wild animals (e.g., bats, raccoons, skunks, and foxes), and larger carnivores are thought rabid if they sneak assault a person, pets and dogs are the main vectors to spread rabies to humans if they are not vaccinated (Liu & Cahill, 2020). As contact with pets, dogs, and other domestic animals cannot be limited, and it is also impossible to eliminate the probability that these animals may associate with rabid vectors, the immunization shot of these animals for pre-exposure prophylaxis is the best strategy to avoid animal rabies. The spread of rabies can be effectively decreased and humans can be protected from the threat of the disease through the repeated immunization shots of pets, dogs, and domestic animals, especially dogs. The public health organizations usually stipulate laws or standards for animal vaccination against rabies to ensure the health and safety of humans and animals. The rabies vaccine is extensively used and beneficial for the prevention of rabies virus infection in humans, but there are some drawbacks arguing even stopping vaccine promotion and spread including incomplete immune responses, adverse effects, multiple dose vaccination requirement, finances, less vaccine supply, and cold sequential dependencies (Fig. 3) (Chen et al., 2025).

Conclusion

As a fatal viral untreatable disease, rabies is a serious public health concern. Rabies is present all around the world but it is a significant issue with high mortality in developing countries. The reason behind this is the large population of dogs, especially unowned or stray dogs. The virus is only transmitted when it gains entrance into a wound, especially a dog bite wound as the virus is present in the saliva of the dog. The only way to protect the population against the virus is to prevent the infection as the virus is untreatable. The best way to prevent the virus from causing disease in animals is to vaccinate the animals and limit the wildlife contact. In humans, it is necessary to raise the knowledge about this fatal disease, how it is transmitted, and the information about the reservoir hosts (wildlife animals). The spread of information about the transmission, prevention, and control of rabies is of great significance. The proper management of unowned dogs should be considered and development of laws and legislation regarding this will help to prevent and eliminate this disease.

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