Rabies: The Scientific Basis and Its Public Threat

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Abstract. Every year, more than 55,000 people die from rabies around the world. Most human rabies deaths happen in Africa and Asia, where rabies remains a neglected disease. As soon as symptoms appear, human rabies is usually fatal due to acute, progressive encephalomyelitis. Although humans take precautions against rabies, sporadic outbreaks still occur in wild populations, indicating that factors that govern virus transmission and spread remain unclear. A great deal is unknown about the evolution of rabies viruses and other lyssaviruses. Because lyssaviruses are highly neurotropic, they infect the nervous system by breaking through the skin barrier. The transmission of rabies is largely dependent on domestic dogs. In addition to being part of the daily lives, domestic dogs are also part of our surroundings, which makes them more likely to contract zoonotic diseases. To eliminate rabies from domestic dog populations, which are the most dangerous vectors for humans, a sustained international commitment is important. Preventing clinical disease and death in domesticated and wild animals can be accomplished by vaccination and avoiding behaviors that may trigger exposure. Vaccines for wildlife and monoclonal antibodies are also being investigated as ongoing treatments.

Keywords: Rabies, Scientific Basis, Prevention and Treatment.

1. Introduction

Rabies is a zoonotic infectious disease, mainly caused by rabies virus. When rabies virus enters the human body, it will destroy the central nervous system of the human body, with a high mortality rate. Multiple historical records span continents and date back more than 4,000 years indicating that rabies is lethal encephalitis caused by lyssaviruses [1]. Dogs or wild carnivorous animals can transmit the disease to humans by biting or scratching them. A large percentage of the time, people who are infected by the rabies virus are infected from wild animals such as coyotes, skunks, raccoons, foxes, and bats. There is, however, a large percentage of those individuals who are infected by the virus who are exposed to it through dog bites, which account for 99% of the cases in which the virus is spread from dogs to humans. It has been proven that rabid animals excrete rhabdoviruses in their saliva when they bite a person. Therefore, the virus spreads through the bloodstream from the wound to the brain after being bitten by an infected animal. When bitten by an infected animal, the virus enters the wound immediately, and it spreads along the nerve tissue to the brain within a matter of seconds. Through nerves, it is transmitted to the salivary glands, resulting in mouth-foaming [2]. Rabies, however, is almost always fatal once the symptoms manifest, regardless of the species. Incubation periods for viruses in dogs can range from one week to several months, depending on the site of infection, the dose, and the strain of the virus. The diagnosis of rabies should not be made solely on the basis of clinical signs, which is due to the many rabies patients develop mute rabies, which is easily overlooked, while others die of the disease without exhibiting any symptoms [3].

It is common for humans to experience symptoms such as lethargy, bodily discomfort, fever, and headache as the first signs of rabies. There may be a few days of discomfort following the onset of these symptoms. Symptoms of cerebral dysfunction, and agitation, may develop within days of a bite, including tingling and scratching. A person with this disease may suffer from abnormal behavior, delirium, and respiratory failure as it progresses [2]. During the incubation period, the infection may be prevented from progressing. It is recommended that the bite site be immediately washed after exposure to a possible diseased animal, followed by one anti-rabies vaccination within 24 hours, followed by four additional doses of vaccine. Moreover, even healthy and generally friendly wild animals may carry rabies if they come into contact with humans or dwellings [3].

For people exposed to rabies, timely, effective and standardized treatment and active and passive immunization can effectively protect rabies exposed patients. With the aim of providing theoretical support for effective prevention and treatment of rabies in health care institutions, this paper summarizes the current epidemiological situation and clinical control measures of rabies from the perspective of epidemiology and clinical control of rabies-exposed populations.

2. Clinical characteristics and transmission

2.1. Morphology of rabies virus

Rabies virus is a rhabdoviridae negative-stranded RNA virus. A host-derived membrane envelopes RABV virions, which have a bullet-shaped shape approximately 200 nanometers by 80 nanometers [4]. In addition to the constraints of budding, there is also the possibility that viral uptake may influence the bullet shape. This virus contains a relatively small number of proteins encoded by the RNA genome (12 kb). The virus consists of five proteins: nucleoproteins (N), phosphoproteins (P), matrix proteins (M), glycoproteins (G) and polymerase (L) [5].

2.2. Life cycle

Three phases are usually involved in the progression of rabies. In early Rabies infection, the Rabies virus attaches to the cell surface via glycoproteins, followed by a pH decrease below 6.2, which triggers an endosome-mediated fusion that releases NC into the cytoplasm of the cell. Upon reaching a certain level of viral N, the second phase of viral replication begins. In addition to serving as a template for viral genome synthesis and mRNA synthesis, positive sense RNA plays a crucial role in the production of viral proteins. Upon maturation, the virus bursts from the cytoplasmic membrane. A virus is able to burst from the host membrane when the RNPs assemble with the M [6].

2.3. Various hosts and transmission

Because the Rabies virus has the ability to infect a variety of mammals, it can infect a wide range of species [7]. In addition to domestic dogs, wildlife, including carnivores and bats, plays an important role in the spread of rabies among humans. It has been demonstrated in the laboratory and in the wild that a number of carnivore and bat species are effective rabies reservoirs. However, the location of many other carnivores and bats remains unknown [8].

In a study conducted by Worsley-Tonks et al., 68 carnivores and nine bat species were found to be known rabies virus reservoirs on the basis of the PanThERIA database and a gradient elevator. Furthermore, RABV reservoirs have been identified in Mexico and the southwest of the United States, based on conservative models. In Central America and northern South America, they may be present, however, according to free models. Mexico, the southeastern and western United States, southern Brazil, and northern Colombia are predicted to have the highest concentrations of reservoirs according to the conservative model. Western Mexico and northwestern South America, on the other hand, are the main regions with reservoirs based on the liberal model. Comparatively to conventional and free models, RABV reservoirs are populations rather than species. In addition to determining which species will act as RABV reservoirs in specific locations, studying reservoirs can also identify those species that will serve as RABV reservoirs throughout their range [8].

2.4. Transmission and pathogenesis

RABV causes lethal infections that persist for less than a week in mammalian hosts that have a relatively long lifespan and slow reproduction rates. To maintain its population levels, the virus relies on transmission within the same species [9]. Most viral transmission occurs through contact with saliva-carrying viruses that pass through the skin barrier to infect, though it can also occur through mucous membrane contact. A retrograde axonal transport will allow the virus to reach neurons in the peripheral nervous system after entering the host. Clinical disease occurs as the virus replicates in the central nervous system and spreads through the brain. Scientists have observed behavioral changes as a result of this disease, and resulting in two outcomes: rage rabies and paralytic rabies.

Before the disease progresses to a paralytic or aggressive stage, incoordination, fever, and inhibitory spasms are likely to be observed. In general, heart failure is considered to be the cause of death, although replication within the brain can result in the failure of multiple organ systems. Despite the lack of pathognomonic symptoms for rabies in humans and animals, the lyssavirus is responsible for the disease and only laboratory confirmation can confirm it. Sometimes, the diagnostic capabilities do not confirm the presence of a particular strain of lyssavirus, thus infection can be attributed to other infectious agents or medical conditions. There have been few human cases associated with these remaining lyssaviruses, and their pathogenesis is unclear [5]. Host immunity as well as the nature of the exposure (e.g., dose, location, and depth of inoculation) can influence the severity of an infection. Comparing bat and carnivore-associated RABV strains is revealing differences in strain levels that impact exposure outcomes [9].

In addition, it is still unknown where RABV originates. It has been shown by phylogenetic analysis that RABV has evolved primarily through host transfer, mainly among bats and carnivores, but transfers between these mammalian phyla have been much rarer. Bats are generally thought to be the source of RABV transmission to carnivores. It is pertinent to note, however, that RABV's evolutionary history is complicated by unexplained observations. This is due to the fact that Old World bats carry lyssa viruses related to RABV, but not RABV itself, while New World bats only carry RABV. The origin of RABV may eventually be revealed through advancing virus discoveries and/or analytical methods [9].

3. Prevention and Treatment

In the absence of clinical signs, rabies is almost always fatal. Only six documented cases have survived [10]. In Asia and Africa, most rabies deaths occur, although rabies can also be found on every continent except Antarctica, according to WHO [18]. It is very important to implement effective intervention and prevention measures to avoid rabies.

3.1. Health education

With the improvement of people's living standards, the number of pets has increased significantly, which also increases the risk of rabies exposure. Therefore, carrying out health education for people, improving people's awareness of prevention and strengthening health education related to rabies prevention and control can effectively promote the timely vaccination rate of rabies vaccine, which is of great value for the final prevention of rabies [11]. Both pre-exposure prophylaxis and post-exposure prophylaxis are included in these treatments.

3.2. Preexposure prophylaxis (PrEP)

Rabies cannot be cured except through supportive care. Vaccination against rabies and rabies immune globulin can be given as soon as possible after contact with saliva or a bite from an infected animal can prevent latent symptoms of rabies. In order to stop the progression of the virus in the nerves, human rabies immune globulin is applied or injected at the site of the bite immediately after the bite. This method attacks the virus and prevents it from moving along the nerves. In view of the supportive nature of rabies treatment, untreated or inadequately treated cases almost always result in death. A new rabies treatment has been developed that provides effective protection against the disease [12].

Some people are more susceptible to rabies exposure than the general population, and for these people, PrEP, a series of human rabies vaccines prior to exposure. A rabies PEP program cannot be totally eliminated by PrEP, but it can be simplified with PrEP. Individuals with different risk classes for rabies exposure should receive different recommendations for PrEP. Activities with the highest risk are classified in the first level, while those with the lowest risk are classified in the fifth level.

Individuals exposed to rabies virus or rabid animals, such as veterinarians, animal breeders, laboratory workers, international tourists who may come into contact with animals in rabies threat areas, etc., are included in these groups. In order to minimize the risk of sudden infection, all of these groups are advised to receive PrEP [12].

3.3. Postexposure prophylaxis (PEP)

Prompt administration of post exposure prophylaxis (PEP) can prevent clinical symptoms PEP consists of wound cleaning, rabies vaccine administration and anti-rabies virus immunoglobulin (RIG) administration in and around the wound the use of RIG is limited for many reasons, and its global use rate is less than 2% of rabies virus exposure.

3.3.1 Monoclonal antibodies

Human medicine is in dire need of biologics to control rabies, and mAbs are growing in popularity. Since the 1990s, there are currently two licensed monoclonal antibodies targeting RABV that can be used as a substitute for RIGs in the PEP protocol. Some candidates have reached clinical trials against RABV. As it is important to note, mAbs are highly specific, can be produced rapidly, and have many other advantages [14]. WHO recommends using multiple mAbs cocktails to target different antigenic sites on the G protein, due to the diversity of RABV bat variants [16].

Rabishield has been approved for human use since 2016. RABV conformational epitope is targeted by Rabishield, a recombinant human mAb (IgG1). A wide range of RABV isolates from the Americas, Europe, Africa, and Asia can be neutralized by Rabishield. In addition, because of its monospecificity, this product is likely to be ineffective against emerging rabies variants and will be susceptible to selecting for mutations that escape the virus [13,14].

As of 2019, Twinrab is the second anti-rabies mAb containing two recombinant mouse mAbs: M777-16-3 and 62-71-3, which bind to different epitopes in rabies glycoprotein, providing adequate protection against viruses caused by mutations in rabies [13].

Additionally, there have been promising results in preclinical models or human clinical trials of other mAb cocktail therapies. As an example, SYN023 consists of two humanized monoclonal antibodies against rabies, CTB-011 and CTB-012, which bind to two distinct antigenic sites on the rabies glycoprotein. CDR grafting was used to convert murine hybridomas into humanized acceptors of 3D11E3 and 7G11A3, and then CHO DG44 cells were transfected with these acceptors to generate CTB-011 and CTB-012. Currently, phase III clinical trials are underway for SYN023. Further studies are needed on these mAbs, as there is limited information available [13,15].

MAbs are thought to be effective because they penetrate the CNS and function through the Fcγ receptors in a way that subsequently reduces viral load in the CNS during the symptomatic phase. In addition, they may modulate CNS inflammation during this phase. MAbs are being tested for the first time in vivo as a treatment for symptomatic rabies. This could pave the way for a new paradigm for rabies treatment [13].

Globally, HRIG and ERIG have not yet been replaced with mAbs for a variety of reasons. In countries with poor economic resources, rabies is a particularly prevalent disease, and the clinical trial phase of these classes of fatal diseases is complex and requires a large number of patients with rabies exposure category III [13].

3.3.2 Oral vaccination of wildlife

A rabies vaccine (ORV) for wild animals reduces the possibility of rabies virus spillover into domestic and human populations and limits the spread of the disease to these populations.

In October 1978, ORV conducted its first test on chicken heads injected with the SAD strain of attenuated rabies virus vaccine [17]. Later, ATTENUTATED rabies vaccines derived from SAD were used in large-scale field trials in several European countries. The oral wildlife vaccine challenges of poxvirus vector recombinant rabies vaccine (V-RG) are met with the V-RG vaccine. Even though this attenuated rabies virus vaccine has proved effective in some countries, its widespread distribution remains controversial. Both non-target species and target species retain residual pathogenicity following vaccination with attenuated rabies virus vaccines. Furthermore, it is possible that wildlife may not respond to attenuated oral rabies vaccines. The development of recombinant vector viruses for rabies vaccines, approved in both Europe and the United States, is therefore being undertaken to eliminate the spread of the virus among wildlife populations. Global demand for a safer and more effective ORV vaccine led to this development. To prevent the spread of the rabies virus from infected reservoirs and to provide additional protection for domesticated animals and humans. Wildlife is now routinely immunized with oral vaccines as a part of rabies management programs worldwide. By using oral rabies vaccines such as RABORAL V-RG appropriately, rabies can reduce its impact on agriculture and public health [17].

4. Conclusions

With the intensification of global environmental change, disease prevention and treatment are also facing new challenges. Because animal bites and scratches can cause rabies and other infectious diseases, this has become a social problem that cannot be ignored and has attracted more and more attention. Globally, rabies causes approximately 59,000 deaths each year. It has been fairly slow to reduce rabies in dogs despite the fact that animal vaccination programs reduce rabies in dogs and eradicating stray dogs significantly reduces rabies in dogs.

The development of more effective ways of vaccination dogs is, however, in progress. Using data analysis to create a data-driven vaccination method, utilizing real-time spatial data to guide healthcare practitioners in the field can reduce rabies rates to a high extent. Additionally, scientists develop promising monoclonal antibodies to prevent rabies. Agriculture and natural ecosystems have proposed alternative approaches and routes for controlling rabies such as oral vaccination for wildlife. Rabies can be transmitted directly from bats to humans, but it is extremely rare. Rabies changes the behavior of the bat so that it encounters people and bites them, which healthy bats (except vampire bats) do not do. It is also possible to use a wildlife vaccine as an alternative. As a result of a variety of complex economic, practical, scientific, ecological, and public perception factors, Vaccination has become a controversial method of reducing disease among wildlife species. Both domestic animals and wildlife have developed protective immune responses following 34 years of oral vaccination. Using rabies vaccines for wildlife was a success because of this discovery, and it should continue to be studied.

Finally, rabies is not only a disease that affects humans, but it also affects wild and domesticated animals, which can cause human infection. In order to estimate the impact of rabies more accurately, the effects on animal populations and the cost of preventing rabies transmission from animals to humans should be included. In addition, science popularization and health education need to be carried out at the same time to improve the awareness of rabies, so as to make it possible to eliminate rabies transmitted from dogs to humans.

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