Rabies A Preventable yet Deadly Disease

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Abstract

Rabies is a communicable animal-borne disease that poses considerable public health challenges around the globe, particularly in developing countries. Rabies is initially transmitted through the saliva of infected mammals via bites, scratches, or open wounds. Although rabies is almost scientifically fatal once clinical symptoms appear, it is highly preventable through timely post-exposure prophylaxis (PEP) and pre-exposure vaccination (PrEP). The disease is most commonly transferred by domestic dogs in areas with high stray animal populations, though wildlife species such as bats, foxes, and raccoons also serve as indicators. The zoonotic nature of rabies makes it specifically challenging to control, as both human and animal health are connected in the transmission activities of this disease. Majority of the human rabies cases occur in rural regions, where availability to veterinary services and human healthcare is limited. The rabies transmission initially occurs when individuals are exposed to infected animals. Despite its preventability, rabies remains responsible for tens of thousands of human deaths annually, especially in regions with low vaccination rates and inadequate medical framework. Rabies can be controlled through broad plans, including mass vaccination of dogs, which serve as the primary reservoir of the disease in many parts of the world.

Keywords: Rabies, Zoonotic disease, Vaccination, Dogs, Public health

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Introduction

Rabies is a lethal zoonotic but preventable viral disease which is caused by a permeable nerve-targeting virus, *Lyssa virus* (Kuzmin & Tordo, 2012). It is transmitted through saliva of infected animal via bites or physical contact with mucous membrane to other animals as this virus resides in saliva of infected animal (Dietzgen, 2012).

Rabies has two types. The first one includes furious form (also known as encephalitic form) and occurs in 85% of rabies cases (Davis et al*.,* 2015). It comes with signs of excitability, water phobia etc (Fooks & Johnson, 2018). The second type is paralytic form (also known as furious form) whose most noticeable symptom is paralysis (Wilde & Kitching, 2017). Once, the infected person shows signs and symptoms of rabies, then it is nearly 100% fatal (Rupprecht & Dietzschold, 2019). That's why, when a person who is bitten by a rabies suspected animal, he must receive rabies vaccine for protection against this deadly virus (Jackson, 2020).

Rabies in urban areas is transmitted by non-vaccinated dogs and cats while wildlife animals which transmit rabies include bats, raccoons, jackals, foxes, skunks etc (Fooks & Johnson, 2018). More than 90% of rabies is caused by dogs (Hampson et al*.,* 2009). Wild animals mostly sustain the cyclicity of this virus and spread it to dogs and other household animals (Davis et al*.,* 2015). In the US, rabies is mostly caused by bats and wild animal bites. About 7 out of 10 deaths occur due to bat bites (Smith et al*.,* 2019). From 2007, U.S. has been declared free of dog bite related rabies (Rupprecht & Dietzschold, 2019). Dog bites commonly cause rabies in Asia and Africa (Singh et al*.,* 2017). This virus causes more than 50,000 human deaths yearly, primarily in Southeast Asia and Africa, with more than 40% of children under the age of 15 (Marston et al*.,* 2013).

The countries that are regarded as rabies free are Ireland, Japan, New Zealand, Sweden, Australia, Belgium, American Samoa, Singapore, Scotland, UK etc (Rupprecht & Dietzschold, 2019). However, the countries that are regarded as rabies-controlled countries are Canada, Hong Kong, United Arab Emirates, United States, Bulgaria, Qatar, Taiwan, Kuwait, Chile, Belarus, Tobago, Grenada etc (Banyard et al*.,* 2018).

1. Virus

The genus *Lyssavirus* which is a negative stranded RNA virus of which rabies virus is a member is a causative agent of rabies (Kuzmin & Tordo, 2012). Rabies virus is a member of the family *Rhabdoviridae* because on electron microscopy it appears in the form of bullet (Davis et al., 2015). Like most negative-stranded RNA viruses, rhabdovirus virions are made up of a highly ordered and stable complex of nucleoprotein and genomic RNA that is housed in a lipid envelope that is taken from the membrane of the host cell (Dietzgen, 2012). With a widespread distribution and a lengthy research history, the rabies virus is the most well-known member of the *Lyssavirus* genus (Kuzmin & Tordo, 2012).

Although these lyssaviruses are typically limited in their geographic range and account for a small percentage of human rabies deaths, they may become more widespread when people invade previously uninhabited areas and ecosystems (Pollin et al., 2013; Wiltzer et al., 2012). Although ecological studies of bats have given most of our current knowledge of these viruses, a number of teams have recently used experimental virology approaches to better understand lyssavirus variety (Nolden et al., 2014; Marston et al., 2013; Pollin et al., 2013; Wiltzer et al., 2012). The nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), the five structural proteins encoded by all rhabdoviruses are N and an RNA-directed RNA polymerase (L). A ribonucleoprotein (RNP), which is the tightly wrapped N-RNA complex, is formed when N wraps the RNA genome. The RNP condenses along with L and P to form the helical nucleocapsid (NC), where as, P is one of the polymerase L's noncatalytic cofactors (Dietzgen, 2012). By encircling the NC, M creates a link between it and the viral envelope (Pollin et al., 2013). The only protein visible on the rhabdovirus envelope's surface is G, a trimeric protein that interacts with M at its cytoplasmic side. It is also the only ligand for cellular contact (Marston et al., 2013; Wiltzer et al., 2012).

2. Species Affected

All mammals are affected by rabies. Some have more chances of getting it which includes skunks, bats, foxes, hamsters, guinea pigs etc. (Fooks & Johnson, 2018). Domestic animals which are affected by rabies are dogs (most commonly affected), cats, ferrets, livestock animals (such as cattle, sheep, goats, horses), rabbits etc (Davis et al., 2015).

4. Zoonotic Impact

Rabies is one of the most well-known zoonotic diseases, causing significant ailment and mortality globally (Hampson et al., 2009). Zoonotic diseases are those that can be transmitted from animals to humans, and rabies is a prime example of how human health is closely connected to animal health (Rupprecht & Dietzschold, 2019). The rabies virus (RabV), which belongs to the *Lyssavirus* genus, initially affects the central nervous system of mammals, leading to encephalitis and, in nearly all cases, death once clinical symptoms appear (Kuzmin & Tordo, 2012). Rabies continues to be a major public health concern, particularly in regions with limited healthcare framework and high densities of stray dogs, the initial indicator of the disease (Singh et al., 2017; Wilde & Kitching, 2017).

4.1. Transmission Dynamics and Risk Factors

Rabies is transmitted via the saliva of infected animals, typically through bites, scratches, or open wounds that come into contact with contaminated saliva (Davis et al., 2015). Although many mammalian species are susceptible to infection, some animals, specifically dogs, are the most common sources of rabies transmission to humans. In fact, dogs account for approximately 99% of all human rabies cases globally, particularly in rural areas of Africa and Asia (Fooks & Johnson, 2018). In developed nations, rabies is less commonly transmitted by domestic animals, with wildlife such as bats, foxes, and raccoons serving as the initial resources (Smith et al., 2019).

It proves to be the challenge for any control efforts simply because the nature of the virus is zoonotic, so an integrated health approach on either human health and animal health takes precedence (Rupprecht & Dietzschold, 2019). This disease can easily be transmitted directly from infected animals to human beings, but on the other hand, it acts as a disease that threatens the general ecosystem where wildlife, in this case bats, play the major role of transmitting the diseases (Fooks & Johnson, 2018). Since rabies is a viral infection that is spread through the saliva of animals is very challenging to eliminate without simultaneously targeting the humans and animals to whom they are exposed (Hampson et al., 2009).

4.2. Public Health Burden and Global Impact

Zoonotic rabies causes extreme public health impacts. The WHO estimated that an average of 59,000 human deaths result from rabies every year. Most of the deaths occur in developing countries. Most of the human infections arise from bites or scratches from rabid domestic dogs (World Health Organization (2023) "Rabies" World Health Organization). Although human rabies almost invariably leads to a terminal condition once the symptoms begin to manifest, postexposure prophylaxis PEP) helps control the situation if received in time-the treatment process also includes wound cleaning and a couple of rounds of anti-rabies vaccinations (Rupprecht & Dietzschold, 2019). Unfortunate for most individuals who have lost their lives because of this plague, these medicinal practices often arrive too late to save their victims as they continue to fall to the advances of the disease in futility (Hampson et al., 2009). This impact of rabies is more pronounced in rural and low-income countries where there lacks veterinary care and stray dog management that aggravate the risk of transmission (Singh et al., 2017). The major source of rabies in such areas is the stray dog population, which is usually not vaccinated. Also, many communities of such endemic regions may not know too much about rabies prevention and transmission, which further heightens delays in treatment following exposure, and consequently, boosts the opportunities for dying (Wilde & Kitching, 2017). Rabies also is the cause of great fear and misery to the affected communities that result in social, psychological, and economic consequences (Rupprecht & Dietzschold, 2019). In most animal outbreaks of rabies, the destruction of affected animals becomes wide-scale and often causes economic dislocations in the locality, more especially to economies dependent on livestock or pets (Rupprecht & Dietzschold, 2019). This fear of the transmission of rabies also affects human willingness to interact with animals and can lead to disruptions in local ecosystems and agricultural practices (Fooks & Johnson, 2018).

4.3. Impact on Animal Populations

Rabies is another important disease that poses a significant problem to the animal population, both regarding the disease and to the mortality of the disease (Fooks & Johnson, 2018). The disease first occurs in the mammals, and the infected animals often become very aggressive, so the chances for transmission to others and to man are increased, and in other cases, even wildlife populations act as reservoirs for the virus, such as foxes, bats, raccoons in spreading the infection over large geographically spread territories (Rupprecht & Dietzschold, 2019). This is particularly significant in the zones of high fauna diversity as foci of infection present an additional difficulty to control rabies cases (Fooks & Johnson, 2018).

For domesticated animals, rabies is a preventable but potentially fatal disase (Hampson et al., 2009). Vaccination of pets, especially dogs, is the most effective method to prevent rabies transmission to humans (Rupprecht & Dietzschold, 2019). Yet, still, millions of dogs in developing countries are unvaccinated against rabies (Hampson et al., 2009). With most transmission occurring in rural areas where the stray population remains the main source of transmission, it is tough to break the cycle of disease transmission without mass vaccination programs (Singh et al., 2017). Besides domestic dogs, other livestock like cattle and goats die of rabies, causing severe loss to the farmers and rural communities (Rupprecht & Dietzschold, 2019). It can cause the breakdown of whole ecosystems by wildlife rabies (Fooks & Johnson, 2018). For example, rabies has done significant damage to bat populations, which are crucially important for insect control and pollination (Smith et al., 2019). Such outbreaks in areas where foxes or raccoons act as disease reservoirs can cause dropping of those species with a falling effect on local biodiversity (Singh et al., 2017).

4.4. One Health Approach and Control Strategies

Due to the zoonotic nature of rabies, a "One Health" approach will be needed because human, animal, and environmental health is interconnected (Rupprecht & Dietzschold, 2019). In this regard, control of the disease will require that there is coordination among the veterinary, medical, and environmental health sectors in the management of risks associated with transmission (Fooks & Johnson, 2018). Mass vaccination campaigns for dogs are the most important component of a control plan because these are the first animals in the transmission cycle to humans (Singh et al., 2017). In areas where rabies is highly dominant, at least 70% of the dog population must be vaccinated to break the transmission cycle and reduce the risk of human cases (Hampson et al., 2009). In addition, public education drives have played key roles in diminishing the zoonotic effects of rabies. These drive instruct such communities on the rationale and importance of vaccination, the manifestations of rabies symptoms in animals, and that prompt treatment should occur immediately after disclosure to minimize infections in humans (Wilde & Kitching, 2017). The other way is that access to rabies vaccines for human cases and animal cases in rural and neglected areas is also an important factor that helps reduce the burden of disease (Rupprecht & Dietzschold, 2019).

Another significant control measure for rabies is controlling stray dogs. In most regions of the world, stray dogs are considered to be the primary source of risk for the transmission of rabies (Hampson et al., 2009). It can be highly reduced by initiating population control for dogs, immunization campaigns, and public education for responsible ownership of pets among the animal as well as human population (Fooks & Johnson, 2018).

5. Pathogenesis

Both humans and animals can contract rabies, a virus that infects the nervous system and typically results in death. Understanding the pathophysiology of rabies has advanced significantly (Jackson, 2020). The rabies virus has influenced both humanity and scientific history since it is one of the few zoonotic viruses known to science to have a nearly 100% death rate once clinical illness manifests (Banyard & Tordo, 2018) . At the molecular level, a viral infection begins when it attaches itself to cell receptors at the bite site and becomes internalized. Besides gangliosides, phospholipids, and glucids, three proteins nicotinic acetylcholine receptor, neuronal cell adhesion molecule, and p75 neurotrophins receptor (p75NTR) have been suggested as rabies virus receptors (Jackson, 2020). There is evidence supporting and contradicting the involvement of p75NTR, which is believed to play a role in the rapid, retrograde axonal transport of rabies virus into neurons and up to the central nervous system (Jackson, 2012). Other, as yet unidentified receptor structures, however, probably facilitate the virus's absorption into permissive cells. Lyssaviruses are extremely neurotropic, and they can reach the central nervous system (CNS) through both retrograde and anterograde axonal virus transports once they have infected the peripheral nervous system (Singh et al., 2017). Viral gene products aggregate in neurons in what are known as "Negri bodies" (NBs), which were the only post-mortem identification for infected people for decades before antibody-based diagnostic methods were developed (Jackson, 2020). The NBs are cytoplasmic round liquid organelles that enable the precise mobilization and accumulation of viral proteins (Banyard & Tordo, 2018). They also carry out cellular antiviral responses, and their development depends on the N and P proteins (Banyard & Tordo, 2018). In order to create new virions growing in the synaptic cleft, viral RNPs are expelled from NBs and carried by microtubules (Jackson, 2020). Trans-synaptic transmission enables the virus to travel along neurons and into the brain (Singh et al., 2017). Virus replication in the brain causes a number of systemic symptoms that point to neurological involvement (Rupprecht & Dietzschold, 2019). Although there are no pathognomonic clinical symptoms for rabies within the clinical spectrum often encountered, several infection-related symptoms (such as hydrophobia and hypersalivation) suggest a possible rabies infection and necessitate definitive laboratory confirmation (Banyard & Tordo, 2018) . Although the time it takes for clinical disease to manifest in humans might vary greatly, it is usually agreed to be between 20 and 90 days after exposure (Jackson, 2020). The causes of this variation are still unknown, and there have been isolated instances where years have passed among the initial exposure and the onset of clinical disease. In any case, the clinical phase is typically shorter (two weeks in humans), and the disease manifests as either paralytic or furious rabies, though even these overlap in the early stages with fever, bite site paraesthesia, and hypersalivation (Singh et al., 2017). After that, furious rabies causes aggressive behavior that is characterized by hydrophobia and sporadic agitation, whereas the paralytic type develops into muscle weakness and paralysis (Banyard & Tordo, 2018). In rabies, interestingly virtually total absence of an inflammatory reaction inside the CNS and neuronal breakdown, instead of neuronal death, may be responsible for the lethal result of rabies under typical circumstances. Despite their defensive role, the immune systems often have pathogenic effects depending on the depth of the disease when immune effectors come into action, especially in the brain tissue (Singh et al., 2017). Because nervous tissue is typically concealed from the immune system, the neurotropic nature of the rabies virus is what causes this process (Singh et al., 2017). Oxidative stress mediates structural alterations involving neuronal processes, which are linked to neuronal dysfunction in rabies (Jackson, 2012). The rabies virus stops NF-κB from being nuclear activated. Increased reactive oxygen species (ROS) production is probably caused by mitochondrial dysfunction. Due to reverse electron transfer, Complex I's increased activity may result in an excess of ROS (Jackson, 2012).

6. Clinical Features

Rabies can be prevented via vaccination through pre-exposure prophylaxis, and post-exposure prophylaxis management before appearance of clinical signs (Rupprecht & Dietzschold, 2019). But when clinical signs of rabies appear in affected animals, then rabies is 100% lethal, and there is no solution or treatment of rabies after arising of clinical signs (Singh et al., 2017). After having contact with rabies virus, this lethal virus propagates, and its destination site is the brain. After reaching the brain, it produces clinical signs (Jackson, 2020). The period in between in having contact with rabies virus and appearance of clinical signs is called as incubation period. It depends on some factors (Banyard & Tordo, 2018).

- Position of exposure spot (Rupprecht & Dietzschold, 2019)
- The extent of exposure with virus (Singh et al., 2017)
- Age of affected animal (young animals have immunocompromised immune system due to which they become more prone to this virus. In same way, older animals have weak immune system due to which they become vulnerable to this virus) (Fooks & Johnson, 2018).
- The affected has undergone through process of vaccination or not. If affected animal has undergone vaccination, then there are less chances of appearance of clinical signs as compared to the animal who has not undergone through the process of vaccination (Hampson et al., 2009).

This incubation period duration fluctuates depending on the position of exposure spot. The closer the exposure spot is to the brain (such as neck or face region), the early clinical signs of rabies appear, and thus shorter is the incubation period. In same way, if exposure spot is far from its destination, which is the brain, the later the clinical features manifest itself and thus longer is it's the incubation period (Jackson, 2020).

6.1. In Humans

The incubation period of rabies has averagely been one to twelve weeks, but it can change from several weeks to months depending on the exposure spot (Rupprecht & Dietzschold, 2019). The earlier sign of rabies is called as prodrome and it includes flu, tiredness, inconvenience, fever, cephalalgia, burning, dullness or itching sensation on the exposure spot (Banyard & Tordo, 2018).

These early signs last for several days and then the main and more lethal signs appear which come in two weeks of initial signs appearance, when this lethal virus cause cognitive impairment. These later signs include insomnia, nervousness, bewilderment, hallucinations, extreme fear of water, fear from light, hypersalivation or foaming at mouth due to immobility of swallowing muscles, convulsion, coma, cardiac arrhythmias, cardiac arrest, encephalitis (Jackson, 2020). These signs and symptoms can vary and will not appear in all cases of rabies disease (Singh et al., 2017). After appearance of these clinical signs, a patient usually dies in two to ten days. Low than twenty cases have been recorded where people have survived from clinical rabies and only few had not undergone vaccination before disease appearance (Rupprecht & Dietzschold, 2019).

6.2. In Animals

The incubation period of rabies in animals is two weeks to three months, but it can change depending on exposure spot and other factors (Fooks & Johnson, 2018). There are two types of rabies in animals which are furious and paralytic form.

Paralytic form of rabies (also known as dumb form of rabies) includes immobility of throat and masseter muscles, difficulty in swallowing, drooping eyelids, labored breathing, abundant salivation (Hampson et al., 2009). Descending of lower jaw is usual in dogs. In this form, animals will not be ferocious and will not try to bite. Paralysis advances to other body parts and it lead to animal death in some hours (Singh et al., 2017).

In furious form, early signs include behavioral changes (such as an aggressive animal become tame/calm, or calm animal becomes aggressive), priapism, fever, anorexia, lethargy, weakness, changes in vocal pattern (such as altered pattern of barking, meowing and other voices), nervousness, in-coordinated movements, dyspnea (Banyard & Tordo, 2018).

Later signs appear after two to seven days of early signs. It include dilated pupils, increased sensitivity to sound or light, extreme fear of water, foaming at the mouth, salivary overproduction, encephalitis, seizures, dysphagia, aggression (affected often attack inanimate things like piercing rocks or trees) (Jackson, 2020). Animal become overly ferocious, attack vaguely, in dog, it is called as mad dog syndrome. Paralysis is uncommonly found in this form (Fooks & Johnson, 2018).

7. Diagnosis

In humans, the clinical diagnosis of rabies begins with a history of exposure to a rabid animal, usually by bite or scratch (Wilde & Kitching, 2017). The initial symptoms may look like many other infections or neurological diseases, hence it is difficult to diagnose (Rupprecht & Dietzschold, 2019). However, as the disease progresses, the symptoms become characteristically hydrophobic, delirious, and paralytic in nature (Jackson, 2020). Some patients may have confirmed diagnosis by a history of exposure to a rabid animal in areas where the disease is endemic.

This means a diagnosis may not be reached based on clinical signs only because such similar symptoms occur in numerous diseases in the neurological category. Laboratory confirmation is therefore required (Banyard & Tordo, 2018).

7.1. Laboratory Diagnosis

The presence of the rabies virus can be ascertained through laboratory tests. There is one test whose outcome has contributed to its wide recognition; this is the direct fluorescent antibody (dFA) test, which measures the antigens of the rabies viruses in tissue samples (Jackson, 2020). It is viewed as the gold standard in establishing the diagnosis of the disease in animals and humans alike. This involves detecting tissue, which is sampled from the brain. It is postmortem diagnosis that is more frequently performed in animals, although this can also be conducted, albeit at the cost of utilizing some human subjects by testing the cornea, saliva, or cerebrospinal fluid (Singh et al., 2017).

Other tests include RT-PCR reverse transcription polymerase chain reaction, detection of the viral RNA in body fluids, and isolation of the virus through tissue culture. These are not frequently used because they take much time and are relatively expensive (Wiltzer et al., 2012). Serological tests can be done wherein specific antibodies for rabies are noted in sera during the later stages of the disease but hardly applied in the early diagnosis of rabies (Banyard & Tordo, 2018).

8. Prevention

Rabies is a preventable disease, and the major approaches to its prevention both use animal as well as human immunization and public health measures (Hampson et al., 2009). The most effective prevention efforts target controlling the animal reservoirs of rabies, particularly dogs, and speedy intervention after exposure (Hampson et al., 2009).

8.1. Animal Vaccination

Because dogs remain the principal mode of rabies transmission to humans, Vaccination of domestic dogs is the cornerstone of rabies control (Singh et al., 2017). Mass dog vaccination campaigns have proven to be very effective in reducing the incidence of rabies in animals and humans (Hampson et al., 2009). According to the World Health Organization (WHO), the vaccination of at least 70% of the dog population in areas where rabies is rampant reduces the virus spread by a significant margin (Hampson et al., 2009). In addition to the above two, vaccinating domestic dogs, another major role is that of regulating stray dog populations. Sterilization and oral vaccinations of stray dogs will definitely prevent new cases and reduce the spreading of the virus (Rupprecht & Dietzschold, 2019).

Oral frameworks for wildlife rabies vaccination have also been employed in cases where there exist wild animals like raccoons, foxes, and bats that could serve as reservoirs for this virus (Smith et al., 2019). Oral programs rely on bait containing rabies vaccines to expose wildlife, reducing the risk to humans (Smith et al., 2019).

8.2. Human Immunization and PEP

It is highly feasible to prevent Rabies in a human by immunization with stages of PEP (Banyard & Tordo, 2018). PEP consists of administration of stages of rabies vaccination, sometimes alongside rabies immunoglobulin administered after an exposed person, in most cases resulting from animal bites (Jackson, 2020).

It is very effective if administered before the onset of symptoms and can prevent onset of symptoms and death (Rupprecht & Dietzschold, 2019). The WHO advises that persons at high risk of exposure such as veterinarians, animal handlers, and travelers to endemic areas receive pre-exposure prophylaxis (PrEP) (Hampson et al., 2009). The PrEP involves receiving a rabies vaccine before potential exposure & it guarantees human safety in cases where an individual touches a rabies-infected dog (Singh et al., 2017).

8.3. Social Mobilization/Community Education

Public health education is the last but not the least important part to prevent rabies in humans (Wilde & Kitching, 2017). Educating the people about how they can save themselves from exposure of diseased animals, that diseased stray dogs themselves are diseased due to rabies, is a very good source for saving themselves from the disease. In those countries and regions where animals are diseased (Fooks & Johnson, 2018).

In a public health campaign, the risk of rabies is often heightened to seek medical attention and vaccines immediately in the hope of diminishing any chance of the infection (Rupprecht & Dietzschold, 2019). Integrating these actions with post-exposure treatment and vaccination programs effectively controls and eventually eradicates the disease, based on the presence of sufficient resources in the area (Hampson et al., 2009).

9. Outcome

Rabies is almost certainly a fatal disease anywhere in the world once clinical symptoms appear, and the danger of rabies infection is almost certain to be fatal without early treatment (Jackson, 2020). The disease runs its course quickly, and although there are some recorded survivors after especially vigorous medical treatment, this is very rare (Fooks et al., 2018). Overall, prognosis remains very poor once clinical symptoms develop (Rupprecht & Dietzschold, 2019).

9.1. Progression of Symptoms

In general, rabies begins with nonspecific symptoms, that is, fever, headache, and malaise similar to other viral infections (Jackson et al., 2018). More defined neurological symptoms, however, can be identified once the virus has reached the central nervous system, especially anxiety, agitation, confusion, hallucinations, hydrophobia, and difficulty swallowing (Banyard & Tordo, 2018). As the disease continues, it triggers paralysis in muscles, and, limbs first take the appearance so that it progresses to the remainder of the body, followed by the muscle responsible for respiration, leading eventually to its breakdown (Fooks et al., 2018). The final stage of rabies includes coma and death, usually triggered by complications like arrest of respiration or heart attack sometime within the period between 2 and 10 days since the onset of symptoms (Fooks et al., 2018).

9.2. Fatal Outcome

Once clinical symptoms present, rabies is almost a 100 percent fatal disease. The virus causes encephalitis (inflammation of the brain) and severe neurological damage, which ultimately leads to death (Fooks et al., 2018). The absence of any effective treatment after the beginning of symptoms is the primary reason for the high death rate (Rupprecht & Dietzschold, 2019). The virus travels along nerve pathways to the brain, where it causes significant impairment of brain function and a range of life-threatening symptoms, including paralysis and seizures. Respiratory failure, typically caused by paralysis of the diaphragm, is the leading cause of death in rabies-infected individuals (Singh et al., 2017).

9.3. Survival Cases

Although rabies has almost always proved fatal once the symptoms appear, there have been a few isolated cases of patients surviving, particularly after they receive extensive supportive care and an experimental treatment called the "Milwaukee Protocol" (Jackson et al*.,* 2018). This protocol provokes coma combined with a package of antiviral drugs. These survival cases are extremely rare. So far, no standard treatment for rabies can be followed if symptoms of rabies are clinically evident (Jackson et al*.,* 2018). These cases do not change the overall poor prognosis for patients infected with rabies (Rupprecht & Dietzschold, 2019).

9.4. Prevention and Outcome

The best result of rabies would be prevention (Hampson et al*.,* 2009). The PEP - post-exposure prophylaxis, which consists of a course of rabies vaccinations and, depending on the time elapsed since exposure to the rabid animal, rabies immune globulin, can prevent the onset of the disease if administered promptly (Banyard & Tordo, 2018). The PEP has been highly effective and has saved countless lives around the world, especially when administered before symptoms. No established treatment can be offered to modify the natural course of disease at onset of symptoms (Jackson et al*.,* 2020).

Conclusion

The outcome of rabies is nearly always fatal after clinical symptoms arise. Death can be avoided if the person in contact manages to come across post-exposure prophylaxis at an early stage, but if the disease has developed to its clinical stage, the prognosis is unfavorable. Hence, preventing death by rabies, it is the vaccination of both animals and human beings and early involvement of medical providers. The effort for global elimination of rabies requires support with a multi-level strategy integrating improvements in access to veterinary and health care, environment management, and more appropriate community mobilization for interrupting the transmission cycle and thus ceasing the death tolls.

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