



Mini Review

Rabies infection in Kidney: A hope for treatment in the future

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(Received 1 June 2021, Accepted 21 June 2021)

Summary

Rabies is a serious zoonotic disease. There are currently no treatment methods to cure, and most of the infected patients die. The rabies virus invades the peripheral and central nervous system (brain), resulting in encephalitis and organ failure. But, besides the nervous system, the rabies virus can also be found in other organs such as kidneys, valves, intestines, heart, corneas, etc., with evidence through organ transplantations. The organ recipients can receive rabies and infect themselves in many countries such as the USA, China, India, France, and Germany. It is also proven that the kidneys are the organs that actually accumulate rabies but are not directly affected by the infection. The lesion of the kidney comes from the indirect effect of rabies encephalitis itself. As some mechanisms of the body and organs consist of pathogenesis, the immune system is dodged by the infectious P-protein or they become latent in the body's dendritic cells or processes glycosylation. Understanding which of these things makes the kidneys not to be directly damaged by rabies, could be a guideline or hope in the future studies related to rabies treatment. And is a case study that must focus on organ transplant cases as well.

keywords: Rabies, Zoonosis, Kidneys, Virus

Introduction

Rabies is a disease caused by the Lyssa Virus, which belongs to the Rhabdoviridae family (Tordo et al., 1988) and is a long-standing virus that has caused encephalitis throughout human history, killing 59,000 people each year (WHO, 2021). The most common cause of human rabies is a rabid mammal's bite or saliva contact with a wound or mucous membranes. Without treatment, the mortality rate is nearly 100%. The public health community is now grappling with the transmission of the rabies virus (RBV) through animal vectors

such as dogs, bats, and wild animals, among others. Animal vector management is a challenge in many nations, particularly Thailand. The inability to monitor stray or ownerless animals is one of the reasons that RBV has been spread so far. There is presently no effective treatment for this condition. Any infection of the central nervous system with the RBV leads to death (Jackson, 2016).

And besides the central nervous system, RBV can also be present in extra-neural organs in infected animals (Jackson et al., 1999), such as kidneys, tongues, intestines, heart, and so on, as well as

organ transplantation cases such as kidney, liver, and lungs (Murphy et al., 1973, Fekadu and Shaddock, 1984, Lu et al., 2018,). The discovery of RBV in these organs has led to further research into the virus's effects and why these organs are not specifically affected by the virus, which would be useful in caring for infected people in the future. Despite the fact that a survey of RBV in the patient's kidneys was identified, no pathogen was found in the renal system. Furthermore, the virus's antigen fractures were only observed in the nerve plexuses (Jackson et al., 1999, Srinivasan et al., 2005), suggesting that the virus may have entered this organ but is unable to expand or is in a restricted area. Although, infection may occur after a kidney or other organ transplant from a rabies patient.

Rabies virus in the kidneys and other related organs

-Organ transplantation

Organ transplantation is a surgical procedure that involves moving an organ from a donor to a recipient for care or to replace an organ that has been lost. This is a common procedure in humans to replace organs that have lost their function. Hearts, kidneys, lungs, liver, pancreas, intestines, thymus glands, corneas, and other organs have all been successfully transplanted in the past, with RBV infection spreading from organ donors to organ recipients all over the world. The cornea, veins, liver, lungs, heart, and kidneys were among the contaminated transplanted organs from 1978 to the year 2018 (Lu et al., 2018).

There are additional evidences of RBV propagation to other organs in both animals and humans (Murphy et al., 1973, Fekadu and Shaddock, 1984, Jackson et al., 2001), as well as evidence from rabies patients' histology and immunohistochemical approaches. The salivary gland, tongue, gastrointestinal tract, heart, adrenal gland, skeletal muscle, and skin were all affected. Rabies virus antigen has been found in a wide

range of cell types, including epithelial cells and muscle fibers. The virus has also been found in organ transplant recipients' nerve plexus.

-Pathogenesis

After being exposed to the disease through a wound by a rabies-infected animal or human, the virus multiplies in the muscles at the site of infection, penetrates nerve terminals, and spreads to the central nervous system via endocytosis (CNS). As a result of this happening, the RBV infects the kidneys. Viruses can divide into any part of the neurological system of the body. Salivary glands and epithelial cell tissue, among other glandular organs, are involved. The antigen of the RBV has been detected in nerve terminals as well as epithelial cells in organ transplant recipients, and the virus has been reported to reproduce and cause infection. Administration of immunosuppressants before the procedure to lessen the possibility of the organ recipient's hypersensitive reaction, make it unable to stop the spread of the RBV infection during organ transplantation (Lu et al., 2018)

-Renal symptom in RBV infected cases

The effect of RBV infection on the kidney was recorded in nine patients in Brazil (Srinivasan et al., 2005); the majority of the rabies patients with renal symptoms had acute renal failure. Six out of nine people were found with an increase in their blood serum creatinine levels. The pathological findings include mild-to-moderate glomerular congestion and mild-to-severe peritubular capillary congestion. Two more patients were found to have acute tubular necrosis. These findings were derived from the effects of acute kidney injury (AKI).

However, the symptoms listed above, such as AKI, were caused by a side consequence of hydrophobia, dehydration, and neurological dysfunction, which is an RBV symptom, rather than RBV infection itself. Other kidney-related test abnormalities, such as low blood salt (hyponatremia) may also be present, a condition

that is induced by a mineral deficiency in the diet (Hemachudha et al., 2002).

Hope for rabies treatment in the future

The kidney is one of the organs that rabies can spread through because of the properties of the cells that are appropriate for virus growth. It is also capable of infecting other creatures. Nonetheless, rabies does not affect this organ. Nephrotic lesions are induced by other clinical symptoms that are not directly related to the virus, according to a case study in Brazil. In which case, we can deduce that the kidneys have systems in place to keep the RBV out. Alternatively, you can divide normally. These processes could be used to treat rabies in the future.

The body's immune to RBV, the evasion of the immune system

When the body is infected by a virus, the body responds with innate immunity to prevent infection from spreading throughout the body. A toll-like receptor (TLR) detects pathogens and stimulates type I (α / β) interferons (IFN) and a number of IFN-stimulated genes to create inflammatory cytokines. TLRs can be expressed by dendritic cells (DCs), macrophages, lymphocytes, or parenchyma cells (Mueller and Rouse, 2008); however, this is not the case with RBV infection, because of being able to go around the immune system.

Rabies enters the body and uses G protein to attach to the acetylcholine receptor before penetrating the muscle. Due to the function of phosphoprotein (P) on the surface of the RBV, the virus can bypass innate protection at this stage and enter the nervous system via the neuromuscular junction. Interferon-beta (IFN- β), myxovirus resistance protein 1 (Mx1), and 2'-5'-oligoadenylate synthetase 1 (Oas1) genes are the main targets of the P protein. When the body is infected with a virus, these genes play a critical role in the immunological response. P protein reduces the expression of several genes (Srithayakumar et al., 2014, Siniscalchi et al., 2010), allowing the RBV to survive from the innate

immunity of the muscles and can enter the nervous system.

It has been reported that the RBV can also use immune cells as a vehicle for movement. In an in vitro study, RBV cultured with activated lymphocyte, could continue to grow normally (Thoulouze et al., 1997). Some strains of RBV are also capable of inserting the genetic material into DCs and transporting DCs, such as CVS and Evelyn Rokitniki Abelseth (ERA) (Senba et al., 2013). These were obtained by testing in mice. An infected animal's body cannot recognize the virus until the genetic material travels into the peripheral nervous system and spreads to the brain and other organs (Senba et al., 2013). The authors suggested that it is in part that the kidneys are not affected by the viral immune response. Since the basal immune system of the kidney is composed of the DCs, macrophages, and lymphocytes, the RBV genetic material can penetrate the kidneys through it. Furthermore, the immune system of the kidneys does not respond to the virus, and thus causes lesions in this organ in early post-symptomatic infections, and also disease in people who have been organ transplanted.

Another proof of the immune system was the evidence from research in Vero cells, a cell line extracted from the African green monkey kidney, which is used to cultivate the RBV. This cell line has the ability to supply the virus. Because the Vero cells utilized in the market were eliminated, it is not like normal kidneys in the natural body. The 9-Mb gene, which was discovered in the 12th pair of chromosomes, is in charge of the type I interferon immune system, which destroys viruses and other pathogens that enter the cell. Due to the loss of 9-Mb, Vero cells are unable to produce interferon beta and alpha, allowing the RBV to persist and develop in the Vero cell (Osada et al., 2014). Interferons are usually created by the body's CMI system in the kidneys of natural human and animal bodies, preventing the virus from spreading in the kidney and causing abnormalities, as do BHK cell lines taken from the kidneys of hamsters. The virus was able to divide and replicate in the culture trays

due to the cell line's inability to produce interferons (Hertzler et al., 2000).

Another study compared the furious and dump strains of rabies in dogs and discovered that the furious strain had more virus particles detected in the brain than the dump strain, which are caused by differing immunological reactions, with the dump having a higher level of immunity than the furious form. This increases the immune system's ability to eliminate the virus from the brain (Shuangshoti et al., 2016). The mechanisms of different immune response are currently unclear; however, it could be related to the animal's own reaction, or probably through controlling the expression of other genes, such as MicroRNA.

Glycosylation of G-Protein

To enter the host cell, the RBV uses an endocytosis pathway involving G-protein glycosylation of the N-glycosyltransferase enzyme. This enzyme is abundant in the nervous system because it is constantly producing neurotransmitters, which necessitates a high level of protein and amino synthesis, both of which require glycosylation by glycosyltransferase. As a result, the nervous system is considered to have a lot of this enzyme. This is a good place for the virus to spread and can carry the illness to the brain (Dietzschold et al., 1985, Wunner, 2007).

The virus can also enter the kidneys via the glycosylation process. As a result, the RBV can cause endocytosis in the kidneys, but nerve current may be reduced. Moreover, as previously indicated, the immune response allows the kidneys to resist infection by allowing the virus to divide within the organ itself.

Case studies from rabies survivors

The only rabies patient in the world that survived, she was treated by coma-induced method, and her body immunized against the virus with antiviral drugs (ribavirin and amantadine). She eventually made it out alive, despite the fact that she is the sole patient who has survived this treatment. However, this provides hope for future treatment. Because, her other essential organs, particularly the kidneys,

which assist in regulating the body's mineral system, water, and electrolyte balance, are unaffected by RBV. Also, with physical treatment, they can heal and return to work regularly, implying that if the virus can be removed from the brain, other essential organs can readily return to normal function and consequently would enable the patient to lead a normal life (Willoughby, 2007). Treatment with the body's immune system, glycosylation process, and resistance of kidney that correlates to the virus removal from the cell, are important factors that should be taken into account in finding a cure for rabies infection in the future.

Discussion

From the past to the present, there is no treatment method for rabies-infected patients. Only supportive treatment and combination therapy are available to prolong the patient's life. Several systems must be used to monitor palliative care. The excretory system and the mineral balance of the body, both of which are controlled by the kidneys, are two of the most critical systems. Patients will eventually die from electrolyte imbalance if we do not maintain this. Rabies vaccination and human immunoglobulin (HRIG) are used as combination therapy to boost the immune system and to eradicate the virus from the body. Immunotherapy with IFN alpha is used as a supplement to antiviral drugs such as Ribavirin in order to remove the virus from the body. These drugs are used in conjunction with the supporting patient's body for treatment (Jackson et al., 2003; CDC, 2020,), but the drug's adverse effects on the kidneys should be addressed. Ribavirin and interferon have been demonstrated to have the following effects on the kidney in previous investigations.

Ribavirin – Ribavirin, an antiviral drug, is commonly used to treat Hepatitis C. It has been shown that patients with renal impairment are less able to excrete Ribavirin through the kidneys. Additionally, the tolerated dose was greater than in patients with normal renal function (Brennan et al., 2013). Hemolysis was a side effect of ribavirin,

which was more common in people with impaired renal function (Jain et al., 2002). This could be concluded that if in the treatment of rabies patients, we were unable to restore normalcy to the kidneys that had not been affected by the RBV, resulting in organ failure due to symptoms. Antiretroviral Ribavirin treatment, like the others that come after it, may fail and make rabies treatment less successful.

Interferon therapy - Interferon is a type of cytokine that plays a role in inflammation. Interferon is used to treat a number of illnesses, including cancer and viral infections. Interferon's side effects, on the other hand, have been recorded in a large number of patients. Interferon therapy, for example, has been shown to cause a nephrotic syndrome in certain people with multiple sclerosis (Kumasaka et al., 2006). Another case of IFN treatment for malignant melanoma resulted in individuals developing nephrotic syndrome and proteinuria after the IFN was stopped without the use of glucocorticoids (Nakao et al., 2002).

In conclusion, rabies treatment using a combination therapy combining rabies vaccine, HRIG, Ribavirin, and IFN alpha can reduce the virus load in the patient's body, although this is limited by the drug's side effects. As a result, the treatment necessitates the preservation of essential organs in order for the body to combat and to eradicate the virus effectively. Because the kidneys are not directly damaged by the RBV, Ribavirin and IFN have a greater impact on them. However, with some treatments, the patient might develop organ failure as a result of symptoms or pharmacological side effects. If the kidneys and other organs can be kept alive, the treatment may become successful. If we can cure rabies in individuals with central nervous system illnesses in the future, we may be able to increase the treatment success rate. With such success, the patient can live a regular life after the treatment.

In addition, one of the major issues with rabies kidneys that should deserve attention is the subject of organ transplantation, which occurs in many

cases, because, as discussed above, rabies is a disease that is difficult to diagnose when a patient is still alive. In this regard, the main symptom is neurological symptoms that may cause rabies to be overlooked since rabies is a very rare disease. Moreover, because it is an organ donor, the transplanted organ might not receive a detailed and specific diagnosis of the disease. Thus, this is a case that should be studied in the future case of organ transplantation.

Acknowledgement

The authors would like to thank all the original articles' authors, whose data were used to write this review article. We also thank Dr. Boonlert Lumlertdacha (DVM), the chief of the Animal Diagnosis and Investigation Department of *Queen Saovabha Memorial Institute*, and *The Thai Red Cross society* for providing very insightful information.

Conflict of interest statement

The authors declare no conflict of interest.

Ethical approval

Not applicable

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