Biological Times Volume No. 4 | Issue No. 7 | Pages 36-37

Neurotropic Nightmare: How Rabies Hijacks the Human Brain

Muhammad Izhar[1*], Sahar[1], Musharraf Manzoor[1], Muhammad Rehan Khalid[2], Saira[1] and Ayesha Bintay Farooq[3]

1. Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
2. Bachelor of Science in Nursing, University of Health Sciences, Lahore, Pakistan
3. Department of Physiology, Government College University, Faisalabad, Pakistan

*Corresponding Author: **muhammadizhar173@gmail.com**

ABSTRACT

Rabies is a disease that infects the central nervous system and causes serious brain damage. The disease is usually spread by the bite of infected animals, specifically stray dogs. Except in Australia and Antarctica, the Rabies virus (RABV) is found everywhere, and every year, almost 60,000 casualties are reported. After entry of the virus into the body, it first replicates in the muscle cells and from muscle cells to nerve cells, and via rapid axonal transport, it travels to the brain. It smashes the brain cells and disturbs the normal function. There are 5 stages of disease, and they appear in two clinical forms, furious and paralytic rabies. The Viral structural proteins N, P, M, and G play a crucial role in the immune evasion strategy after interrupting the antiviral responses, reducing inflammation, and keeping the blood-brain barrier undamaged. By studying these mechanisms for enhancing treatment, one can reduce the chance of neurotropic viruses.

Keywords: RABV, axonal transport, furious rabies, paralytic rabies, structural proteins

To cite this article: Izhar M, Sahar, M Manzoor, MR Khalid, Saira & AB Farooq. Neurotropic Nightmare: How Rabies Hijacks the Human Brain. Biological Times. 2025. July 4(7): 36-37.

Introduction

Rabies is a zoonotic disease that attacks the CNS and causes inflammation of the brain and spinal cord. It is a fatal Viral disease that has spread over 150 countries in the world and results in millions of deaths, mostly in Asia and Africa. Out of the total cases, 40% of the affected individuals are children under the age of 15. RABV can be found in stray dogs, flaps, raccoons, pigs, and bats, but stray dogs can contribute 99% of the total rabies spread in individuals [1]. RABV is one of the deadliest infectious agents, with an approximate economic cost of $8.6 a year and cause almost 60,000 fatalities annually around the world. It has been recorded in every continent with exception of Antarctica and Australia. It may be passed by bite, by licking of a wound, and by scratching. Rabies virus is a single-stranded, negative-stranded RNA virus (ssRNA), genus Lyssavirus, and family *Rhabdoviridae*, and it infects both warm-blooded and domestic animals [2].

RABV particle is normally around 60 nm in diameter and 180 nm in length. It has a single-stranded RNA genome, and it has five proteins regarded as essential to viral functioning, namely: glycoprotein (G), matrix protein (M), nucleoprotein (N), phosphoprotein (P), and the large RNA polymerase (L) protein. Combining two proteins, M and N, gives the virus a bullet-like shape. The virus budding process is done by the M protein [6]. The spikes of trimeric glycoprotein (G) play an important role in the virus's entry into the host cell, which is integrated into the virus's outer envelope. Inside, the core structure referred to as nucleocapsid is located internally, formed of the RNA genome, which is surrounded by the nucleoprotein (N), which is coupled with the RNA-dependent L and P RNA polymerase complex. The M protein also helps in connecting the nucleocapsid with the envelope and provides structural stability to the Viral particle. There are many ways of virus spreading, such as scratching, biting, and licking wounds [3,4].

Neuropathogenesis of Rabies

The saliva of an infected animal allows the virus to enter the host cell. RABV first binds with certain receptors present on muscle cells, such as nicotinic acetylcholine receptors, neural cell adhesion molecules (NCAM), nerve growth factor (NGF), and now it enters the muscle cell and replicates. At the neuromuscular junction, the RABV binds with nicotinic acetylcholine receptors to reach the brain. Once the virus enters the motor or sensory nerve endings, it is moved along to the central nervous system using a mechanism known as retrograde fast axonal transport, moving at a speed of about 12 to 100 mm per day. Upon the entry of the virus into the peripheral nervous system, it is directed towards the spinal cord, reaching the dorsal root ganglia where it multiplies further. This replication enables it to spread quickly into the rostral gray matter within the spinal cord. When the virus infects neurons in the spinal cord or brainstem, it can then spread quickly throughout the brain using the network of neuroanatomical connections and axonal pathways. To reach the brain, the exoplasmic transport occurs along the ascending and the descending neural pathways. The virus first attacks the brain stem, and thereafter it will spread to other regions of the brain. Contrary to the case of cell death that is observed with necrosis or apoptosis, it seems that the neurological dysfunction that characterizes rabies is more a result of functional disturbance of the nerve cells, even though the processes involved are not yet well understood [1,5]. Rabies follows five stages, and they include incubation, prodromal phase, acute neurological signs, coma, and is normally followed by death [1,9].

Virus phases

The incubation period of rabies in dogs and cats is highly variable, ranging around 10 days to 6 months, and most occur within 1 month to 2 months. In humans, it is between 2 weeks to 6 years, with a mean of 2-3 months. The duration depends upon some factors like site, depth, and severity of the wound. The initial symptoms are fever and abnormal feelings such as tingling or burning on the bitten area [7,8]. The prodromal stage is characterized by abnormal feelings around the area of the infection, as well as overall body discomfort. People can have a feeling of anxiety, depressed mood, irritability, nausea, loss of appetite, and hypersensitivity to light, sound or changes in temperature [9]. When the infection gets to the central nervous system, it causes a lethal inflammation of the brain and spinal cord that causes either furious or paralytic rabies [7]. It is at this time of the disease that two clinical forms occurred:

Furious Rabies

The most common rabies is furious, which is responsible for more than 80% of human infections. It is marked by intense agitation, increased reflexes, hallucinations, and erratic or violent behavior. One of the most recognizable symptoms is hydrophobia, a fear of water, which results from painful spasms in the throat muscles and difficulty in swallowing. With the progress of the condition, a patient can observe muscle twitching, seizures, and, finally, paralysis [1,7]. A more subtle onset also characterizes this less common form, which is also diagnosed in approximately 20 percent of the cases.

Paralytic (Dumb) Rabies

A more subtle onset also characterizes this less common form, which is also diagnosed in approximately 20 percent of the cases. Instead of hyperactivity, affected individuals show progressive muscle weakness and paralysis, usually starting from the limb where the virus was introduced and then spreading. As compared to furious rabies, patients are not usually aggressive. At this phase, the virus can spread outside the brain to the peripheral nervous system and to other body tissues, and thus infection occurs to other hosts. Once it infects the brain stem, the virus spreads through cranial nerves like facial nerve and glossopharyngeal nerve to get to the salivary glands where it multiplies and gets excreted in large quantities through saliva. Based on this, the virus is also capable of infecting the organs under the autonomic nervous system like the heart, liver, kidneys, and organs in the eye, like the retina and cornea. In extremely uncommon cases, rabies has been passed on via corneal transplants.

The virus often accumulates at sensory nerve endings located near hair follicles at the back of the neck. As a result, skin biopsies from this area are commonly used in laboratory diagnosis. Coma, respiratory arrest, and death occur in the last stage of rabies because of severe neurological deterioration. Blood pressure instability and unstable heart rate may be the outcomes of the failure of the autonomic system. Rabies causes damage mainly through its direct relationship with the immune system of the host and neurons. At the same time, the body's immune reaction in the CNS generates inflammation, which may enhance tissue injury [1].

RABV's Immune Evasion Tactics

The structural proteins of RABV are important in assisting the virus to evade recognition and clearance by the host immune system. There are two positions on two amino acids 273 or 394, in the nucleoprotein (N protein) that are important in inhibiting RIG-I-mediated immune signaling pathway, which blocks the induction of type I interferons (IFNs) and the induction of inflammatory chemokines such as CXCL10 [6]. RABV matrix protein (M protein) also possesses immune-modulatory activity. It binds with RelAp43 being a member of the NF-kB transcription factor family, which results in Inhibition of NF-kB signaling and subsequent decrease in the expression of IFN- beta resulting in evasion of the host immune responses. Besides, the 95 amino acids of the M protein limit at the formation of stress granule, which plays a vital role in antiviral protection. RABV also inhibits immune responses via the collaborative activity of the M and phosphoprotein (P protein). In union, they prevent the activation of the JAK-STAT signaling pathway by keeping the phosphorylated STAT1 in the cytosol, blocking the interferon responses. The P protein also disrupts the TANK-binding kinase 1 (TBK1) and IKKe pathways, which are required in the phosphorylation of IRF-3/7 and therefore hamper the production of IFN [10,11]. Furthermore, P protein does not allow STAT1 and

STAT2 to enter the cell nucleus, disrupting the response to type I and II interferons. It can also bind to STAT3, hindering its nuclear transport and interrupting signal cascades of IL-6. An example of such is P2, which has been found to be highly effective in inhibiting the expression of interferon-stimulated genes (ISGs) much more than P1. P3 version impedes the entry of STAT1 into the nucleus based on the microtubule structures and the oligomeric state of the P protein. Furthermore, P3 binds with promyelocytic leukemia protein, the antiviral product of ISG, which renders the protective effect of this factor nullified. It is also possible that RABV suppresses the production of IFN- y through the mechanism of epigenetic changes like DNA methylation or acetylation of histones [12,13]. Although rabies shows severe neurological manifestations, the virus induces little destruction of the CNS structure. This means that RABV uses the tactics of immune evasion to aid the survival of the neurons and to increase viral transmission. The virus at an infected site can cause apoptosis of CD4+ and CD8+ T cells, but does not infect the neuron or any other immune cells, including natural killer cells, macrophages, and astrocytes. The infected motor neurons elevate the number of Fas ligand (FasL) to bind to the Fas-positive T cells, resulting in their programmed cell death [14]. Apoptosis may suppress viral proliferation, but RABV does not necessarily cause neuronal death to favour its prolonged persistence. Surprisingly, activation of G protein is associated with augmentation of apoptosis, suggesting that it can be a regulator of cell death in a regulatory manner. G protein has a PDZ-binding motif (PBM) which binds with host proteins, i.e. microtubule-associated serine-threonine kinase 2 and protein tyrosine phosphatase, which influences neuronal survival or apoptosis. The P protein of wild-type strains is especially essential in reducing BBB disruption to support immune evasion [15].

Conclusion

Rabies remains one of the deadliest viral infections that is characterized by silent infections, but almost invariably fatal when signs and symptoms manifest. RABV has an advanced mechanism of infecting the nervous system, first developing in the muscle before proceeding along the nerve routes to the brain, where it disrupts normal operation, but without significant destruction of most infected cells. The structural proteins of the virus N, P, M, and G are critical in hampering host defences by suppressing signals of interferons, damping inflammation, and preserving the integrity of the blood-brain barrier to accelerate the spread of the virus without recruiting deadly immune action. Despite impressive advancements in understanding the mechanisms of RABV, no curative intervention can be provided following the development of symptoms. Given the future perspectives, studies need to turn to the new therapeutic approaches, including gene editing technologies, monoclonal antibodies, or future-generation vaccines. Such methods show potential for combating the strategies of viral evasion and could lead to the elimination of rabies on a global scale.

References

[1] Fatima M, Iqbal T, Shaheen L, Salma U, Siddique R, Ali R, Rehman AU, Usman S. Transmission dynamics of rabies virus. Int J Agric Biosci. 2023; 3:386-97.

[2] Qureshi MA, Fatima Z, Muqadas ML, Najaf DE. Rabies; A Potential Human Threat. Biological Times. 2023 Mar;2(3):9-10.

[3] Yankowski C. Formulation of the Rabies Virus Vaccine Vector Against Emerging Viruses (Doctoral dissertation, Thomas Jefferson University).

[4] Ghassemi S, Pourbadie HG, Prehaud C, Lafon M, Sayyah M. Role of the glycoprotein thorns in anxious effects of rabies virus: Evidence from an animal study. Brain Research Bulletin. 2022 Jul 1; 185:107-16.

[5] Farihah IH, NR AD, Arsiazi BA, Nabila C, Anggrayani P. Neuropathogenesis of human rabies. KESANS: International Journal of Health and Science. 2022 Jan 21;1(4):376-86.

[6] Wang PH, Xing L. The roles of rabies virus structural proteins in immune evasion and implications for vaccine development. Canadian journal of microbiology. 2024 Sep 19;70(11):461-9.

[7] Dattaray D. BREAKING RABIES BOUNDARIES.

[8] Kumar A, Bhatt S, Kumar A, Rana T. Canine rabies: An epidemiological significance, pathogenesis, diagnosis, prevention, and public health issues. Comparative immunology, microbiology and infectious diseases. 2023 Jun 1; 97:101992.

[9] Gulzar MW, Maqsood R, Zain M, Suleman M, Rehman TU, Asif S, Wadood A, Hussain J. Beyond fear: A comprehensive exploration of rabies virus and its implications. Hosts and Viruses. 2024; 11:09-19.

[10] Zandi F, Khalaj V, Goshadrou F, Meyfour A, Gholami A, Enayati S, Mehranfar M, Rahmati S, Kheiri EV, Badie HG, Vaziri B. Rabies virus matrix protein targets host actin cytoskeleton: a protein–protein interaction analysis. Pathogens and Disease. 2021 Feb;79(1): ftaa075.

[11] Zhang H, Huang J, Song Y, Liu X, Qian M, Huang P, Li Y, Zhao L, Wang H. Regulation of innate immune responses by rabies virus. Animal Models and Experimental Medicine. 2022 Oct;5(5):418-29.

[12] Zhan J, Watts E, Brice AM, Metcalfe RD, Rozario AM, Sethi A, Yan F, Bell TD, Griffin MD, Moseley GW, Gooley PR. Molecular basis of functional effects of phosphorylation of the C-terminal domain of the rabies virus P protein. Journal of Virology. 2022 May 11;96(9): e00111-22.

[13] Sethi A, Rawlinson SM, Dubey A, Ang CS, Choi YH, Yan F, Okada K, Rozario AM, Brice AM, Ito N, Williamson NA. Structural insights into the multifunctionality of rabies virus P3 protein. Proceedings of the National Academy of Sciences. 2023 Apr 4;120(14): e2217066120.

[14] Kiflu AB. The immune escape strategy of Rabies virus and its pathogenicity mechanisms. Viruses. 2024 Nov 14;16(11):1774.

[15] Ghassemi S, Asgari T, Pourbadie HG, Prehaud C, Lafon M, Naderi N, Gholami A, Azadmanesh K, Sayyah M. Rabies virus glycoprotein enhances spatial memory via the PDZ binding motif. Journal of NeuroVirology. 2021 Jun;27(3):434-43.