ISSN (Print 0974-2115) (Online 2349-8552)
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Rabies, Scientific review in the pathogenesis of disease and its management

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ABSTRACT

Rabies is the most dangerous viral zoonotic disease as its effects on a wide range of warm-blooded hosts and its pathogenesis way. The interaction between the virus and the host has a role in the continuance of the disease. The rabies is an infectious disease caused by the lyssa virus and the infection by this virus is fatal in the absence of immune response.

Our article reviews the transmission, pathogenesis, control, prevention and treatment of rabies and the importance of preventive methods that could be taken to deal with this infection.

KEY WORDS: Rabies, Lyssa virus, Transmission, Pathogenesis, Vaccine.

1. INTRODUCTION

Rabies is a worldwide disease that distributed in all continents except Antarctica, more than 95% of human deaths occur in Asia and Africa and it is considered a Neglected Tropical disease and causes about 59 000 human deaths yearly in over 150 countries. Rabies is one of the Neglected Tropical Diseases (NTD) that affects poor people who live in rural regions. Although effective vaccines and immunoglobulin are existing they are not accessible to those in need. It is usually found in wild animals such as dogs, skunks, bats, raccoons and foxes. In around the world, most rabies death cases happen because of dog bites (Walker, 2018).

Rabies is a disease caused lyssavirus genus of the Rhabdoviridae family (Iqra Bano, 2016; Riedel, 2019). Lyssa virus has a bullet-like shape with a diameter of 75 nm and range in length from 100–300 nm. Lyssa virus consists of the single-stranded genomic RNA, which is tightly bound by the nucleocapsid (N) protein which they form together with the ribonucleoprotein complex (RNP) and takes a helical shape inside the virus. Virion-associated RNA polymerase (L) and phosphoprotein (P) are associated with the ribonucleoprotein complex forming the capsid. The virus is surrounded by lipid bilayer membrane with glycoprotein (G) spikes which cover the surface of the membrane and cross it to associate with the matrix (M) protein (Anthony and Alan, 2020; Alan, 2011; Rameshwar Nath Chaurasia, 2014; Benjamin, 2015).

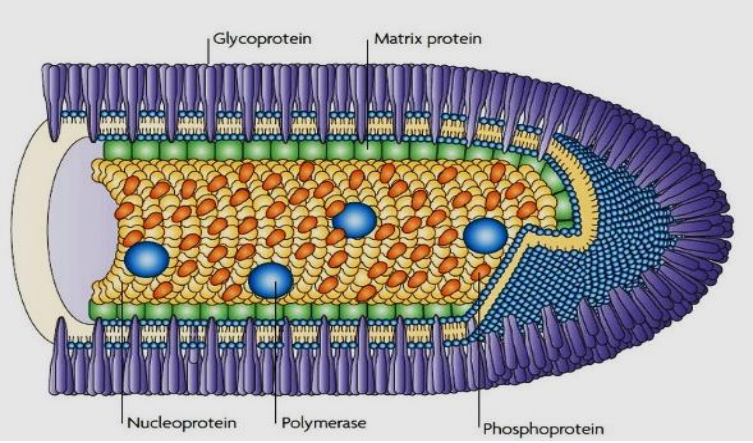

Fig.1. Schematic representation of lyssa virus (Albertini, 2011)

The Viral Cycle: After binding to the host cell receptor, the virus passes into the cell via the endocytic pathway. According to the acidity of the endosome, changes in G protein conformation are happened to allow the fusion of the viral envelope with the cell membrane of the host. Then, The RNP complex is released in the cytoplasm and play a role as a template for viral gene expression and replication in the presence of viral RNA polymerase. Studies showed that RABV transcription and replication take place within Negri bodies which are inclusion bodies that formed during viral infection. The replication process produces nucleocapsids that used for the synthesis of genome-sense RNA. During that, the nascent antigenome is encapsidated by P-L-N proteins complex to form new RNP complexes. The encapsidated RNP goes to the host cell membrane where the M and G proteins are abundant. Once condensation of M protein begins, budding stars from the host cell membrane and this is the final step of replication and releasing of formed virions which are now capable to infect other host cells then repeating the cycle all over again (Benjamin, 2015; Albertini, 2011; Piccinnotti and Whelan, 2016).

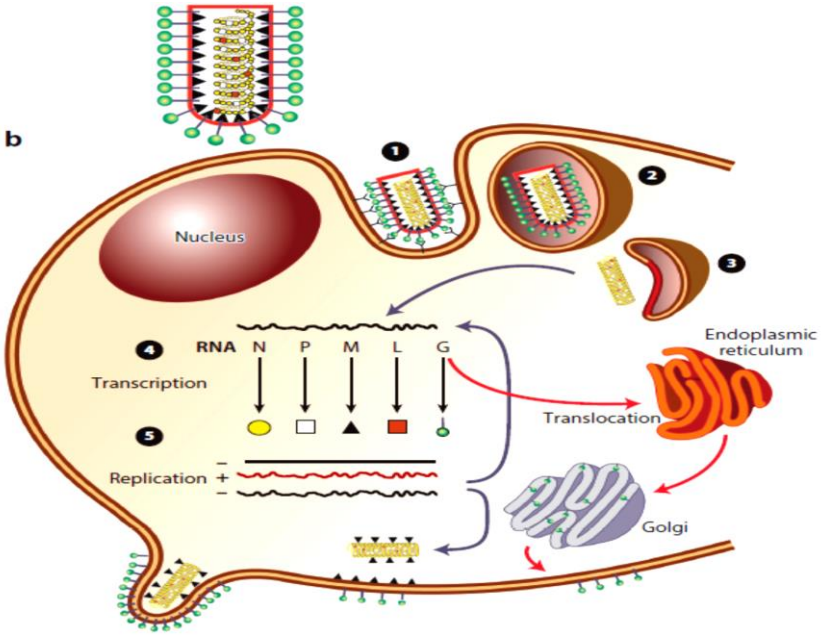

Fig.2. Viral Cycle (Albertini, 2011)

The Way of Rabies Virus Infection through the Host: In most human with RABV, the infection accrues as a result of animal bites causing expose of the muscle tissue to animal saliva that containing RABV. After the bite, the rabies virus stays in the calm phase, in this case, it is hard to be easily detected. During that, it replicates in non-nervous tissue such as muscle. The rabies virus combines to receptors for neurotransmitters accessing to peripheral neurons. Then, it reaches the spinal cord and central nervous system by distributing along nerves, it moves rapidly to the brain through synaptic connections (Figure.3). RABV may be spread from the central nervous system into several organs such as kidneys, heart, ovaries, testes, prostate, heart, adrenal glands and salivary glands (Albertini, 2011; Alan, 2002; Clemennt, 2013; Ugolini, 2011; Macedo, 2006; Piccinnotti and Whelan, 2016; Wijaya, 2017).

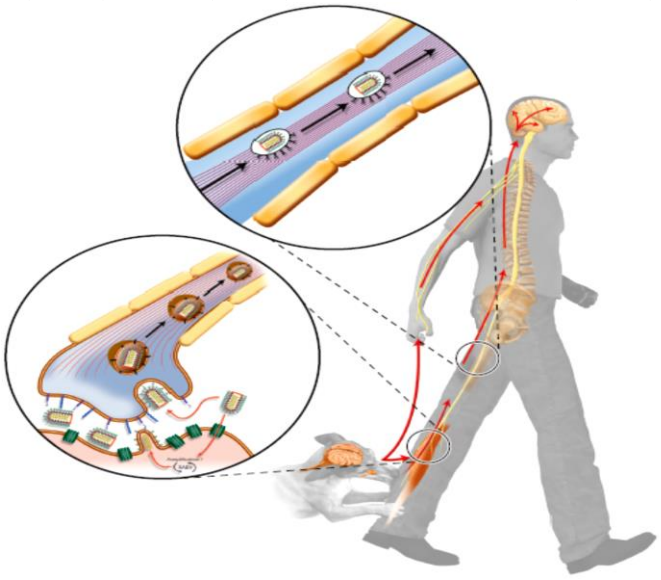

Fig.3. The path of rabies virus infection through the host (Albertini, 2011)

The intrinsic immunity is the first response to pathogenic infection producing interferon α/β and chemokines. It is thought that Toll-like receptors are important pathogen recognition receptors (Alan, 2002), it has been noticed that the human neurons express the TLR-3 molecule when they are infected with some viruses such as Rabies virus. Interferon β, chemokines and inflammatory cytokines are produced from infected cells by stimulating TLR-3. Many studies indicate that the receptor contributes to evolving some of the inclusion bodies (IBs) that are consist of viral N and P proteins.

However, one of the most surprising facts about rabies immunopathology is the almost complete absence of a response within the central nervous system. Maybe it's because of the intrinsic capacity of this virus to avoid the innate immune response of infected muscle cells and infected neurons, besides, to get rid T cells which migrate into the nervous system (NS) by the regulation of immunoevasive molecule PD-L1 and limiting the inflammation in nervous system tissues (Zhang, 2013; Both, 2012; Naoto, 2016; Rieder, 2011; Consales, 2007; Natasha, 2015).

Signs and Symptoms: After a bite, the rabies virus travels through the body to the brain before appearing any symptoms, this stage of infection is known as incubation period which lasts for weeks to months and may vary according to the location of bite (how spacing from the brain) and presence of immunity and viral load. The first symptoms include weakness, fever with pain and burning sensation at the wound site, anxiety, headache. These symptoms may last for days. Then, neurologic symptoms start to be appearing including convulsions, producing a lot of saliva, hallucinations, fear of light, hydrophobia, permanent erection in males, at the end of this stage, breathing becomes more rapid and unstable. In some cases, the person enters a coma and death will occur within a few hours (Walker, 2018; Riedel, 2019; Alan, 2011; Benjamin, 2015; Natasha, 2015; Alan, 2003; 2000; Xavier Lahaye, 2009).
Diagnosis: The rabies virus may be detected in body fluids such as saliva, cerebrospinal fluid. Samples are taken from throat, nasal mucosa or eye and biopsies from skin or tissues of the brain. Histologic examination of biopsy is useful in observation the histological changes and diagnosing of unsuspected injuries with rabies, the unusual changes include Mononuclear infiltration, Lymphocytic foci, cuffing of lymphocytes, Babes nodules with glial cells. Negri bodies are considered as distinguishing feature for rabies virus infection, they take under light microscopy in round or oval shape and stain with pink with haematoxylin-eosin and red with Mann's stain (Riedel, 2019; Alan, 2011; Benjamin, 2015; Ugloni, 2011; Xavier Lahaye, 2009; Whitfield, 2001). The fluorescent antibody test is the most used test for rabies diagnosis. This test is recommended by both the World Health Organization and the World Organization for Animal Health and gives more than 95-99% accuracy within a few hours (Shankar, 2009; Singathia, 2012).

Rabies virus may be diagnosed serologically according to the presence of antibodies in the blood of unvaccinated patients. However, these antibodies aren't detected until the second week of infection, or until death in some cases. Additionally, there are several used methods such as Enzyme-Linked Immunosorbent Assay, Counter Immune Electrophoresis, Immunoperoxidase Test but the more successful method for rabies virus detection is reverse transcription-polymerase chain reaction (RT-PCR) which is characterized by sensitivity and specificity. For this test, the samples are collected from saliva, skin biopsies, Cerebrospinal fluid and brain tissue and takes about four hours (Benjamin, 2015; Natasha and Nisha, 2015; Charles and Thirumeni, 2015; Rajendra Singh, 2017; Charles, 2018; Hue-Ying Chiou, 2016; Aravindh Babu, 2014; Netravathi, 2015; Wasniewski and Cliquet, 2012; Babu, 2012).
Treatment: Rabies is almost fatal once clinical signs appear. Till now, there is no treatment for rabies. In most of the reported cases, the antiviral therapy with cytosine arabinoside or ribavirin has been unsuccessful. Rabies vaccine may not be effective and there are doubts about its detrimental effects. Rabies vaccines do not stimulate a cytotoxic T-cell response which is important for dealing with rabies virus infection (Benjamin, 2015). The CDC recommends to take a dose of human being rabies immunoglobulin (HRIG) in the region of on the day the bites, and then a dose of vaccine given again on days 3, 7, and 14. The combination of human rabies immune globulin and vaccine is recommended in case of a bite or non-bite exposure. There are three rabies vaccines, rabies vaccine adsorbed human diploid cell rabies vaccine and purified chick embryo cell vaccine. The vaccine produces antibodies against rabies virus from 7 to 10 days. Then, the four subsequent doses should be given on days 3, 7, 14, and 28. Neurological symptoms may be reduced by using sedatives, antiepileptic medications and neuromuscular blockers (Riedel, 2019; Alan, 2011; Rameshwar Nath Chaurasia, 2014; Benjamin, 2015; Natasha and Nisha, 2015; Alan, 2003; 2000; Xavier Lahaye, 2009; Jentes, 2014; Weant and Baker, 2013; Daniel and Julia, 2004; Dacheux, 2012; Beyene, 2018).

It's worth mentioning that the pre-exposure vaccination is very effective for people who are continuous contacting with an infected animal such as veterinarians or who live in areas with a high spread of rabies (Warrell, 2012).
Prevention and Control: The important step for prevention of rabies is good animal management including vaccination of animals, avoiding wild animal. The bite wound must be washed with soap and water. Quaternary ammonium compounds such as 1 - 4% benzalkonium chloride or 1% cetrimonium bromide are useful in inactivating the rabies virus. Animal control officers must handle carefully with infected animals or when autopsies and wearing rubber gloves, plastic apron. (Walker, 2018; Riedel, 2019; Alan, 2011; Benjamin, 2015; Xavier Lahaye, 2009; Charles, 2018).

2. CONCLUSION
Rabies is still a main public health problem in many developing countries in the world. The weak of prevention measures, incorrect management of bite and poor availability of therapy are major factors leading to rabies outbreaks around the world, so it is recommended to prevent and control rabies in both before and after potential rabies virus exposure.

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