RABIES - “A NEURONAL DIESEASE”

Abstract

This world is filled with perpetual diseases which are Fascinated by mankind and rabies occupied annon-concessive position even in the present day. Rabies is a zoonotic viral disease caused by Rabies virus (RABV) genotype 1 and this most common lethal infection worldwide. This fear is not due to the incidence it is due to the inevitable clinical signs; the image of furious rabid animal is prepared to bite anything in the path is at the heart of the fear in people who lives in western countries, like Europe, Asia Africa and with bats in America. This chapter gives a explain about the path physiology of the rabies virus.

Keywords: Rabies , RABV, Encephalitic Rabies

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I. INTRODUCTION

Rabies is a terrifying infectious disease of antiquity and currently ranks in the top ten infections killers of human. The true burden of the disease is unknown because the rabies virus is neglected **[1]**. Identification and diagnosis of rabies requires a specialized laboratory. According to the reports, extrapolating the reports from the rate of rabies we found that 500000 people are annually affected by dog bites and dog attack around Africa and Asia (Rodney E Willoughby jr). Rabies is caused by rabies virus (RABV) genotype 1[**2**]. Genotype 1 is said to the most common fatal infectious type which is said to spread worldwide. This type of virus affects the two-third of the human population, remaining of the population is said to be affected by paralytic rabies. Rabies associated with bat RABV has atypical features which is produced by Horner’s syndrome.

Rabies causes viral encephalitis which kills up to 70000 people/year worldwide. Infected animal saliva transmits viral encephalitis to humans **[3**]. Rabies is one of the oldest known diseases in history with cases dating back to 4000 years ago. For most of human history, a bite from a rabid animal was uniformly fatal. In the past, people were so scared of rabies that after being bitten by a potentially rabid animal, many would commit suicide. This is the most common lethal infection worldwide **[4]**.

Rabies develops symptoms – Anxiety, sleeplessness, hallucinations. Panic attack and aggression. The rapid aggression of rabies death accesses within 5 to 7 days of attack or bite, while the death is medically violent- where the death occurs by respiratory spasms and profound swings in temperature, blood pressure with increase in heart rate and leads to death (Rodney E Willoughby jr). Majority of rabies disease are said to be curable, but the bat bites are said to be unrecognized **[5]**. In North America rabies are said to be endemic in wild life and the bat bites are said to be a serious threat to infectious transmission to humans.

This fear is not due to the incidence it is due to the inevitable clinical signs; the image of the furious rabid animal is prepared to anything in the path is at the heart of fear in people who lives in the western countries, like Europe, Asia, Africa and with the bats in America two third of the patients are infected with dog RABV variant is present in the classic raging rabies and this disease was described centuries ago by scientists. a well recorded**[6]**. Book by Theodories in (1986) which focused on the seminal work of Pasteur’s Work, Galtier developed the first rabies vaccine at that time. Current knowledge about Rabies has also been well described by Campbell and Charlton in 1988. Progress has been made in recent years about determining the molecular structure of the virus, the molecular biology of its replication and immunological way and Vaccinations**[7]**. But after this all efforts the rabies virus infection is still not well understood

II. ETIOLOGY OF RABIES

Rabies is the disease caused by the lyssa viruses belonging to the family rhabdoviruses. The cells of these viruses are bullet shaped and these viruses contain negative stranded RNA genome and these viruses are stable drying lyssa viruses **[8]**. Rhabdoviruses include rabies and bat lyssaviruses.

Rabies is transmitted mostly by the bit of a rabid animal which include dog, cat, monkey, bat etc. Rabies is a preventable disease by undergoing proper clinical treatment. RABV affects the central nervous system by affecting the nicotine acetylcholine receptor and this ultimately causing neurological disease and this leads to death if untreated **[9].**

III. STRUCTURE OF THE RABIES VIRUSES

Viruses belonging to the rhabdoviruses are approximately 75nm wide and 180nm wide. All the viruses belonging to the rhabdoviruses have two major structural components, they are a) ribonucleoprotein and b) envelope surrounding the nucleoprotein **[10].**

The genome of the rabies encodes five protein nucleoprotein (N), phosphoprotein(P), glycoprotein(G), matrix protein (M), and polymerase enzyme (L). The genomic RNA of the rabies virus is encased tightly by the nucleoprotein **[11]**.

The P protein and the L protein (polymerase) are associated with the ribonucleoprotein. The genomic RNA is enclosed by the nucleoprotein outer layer the glycoprotein of the rabies forms 400 trimeric unit these units bound around the surface of the virus these glycoproteins are soluble glycoproteinsthe membrane protein is associated with the outer envelope and the ribonucleoprotein acts as the central protein of the rhabdoviruses [12].

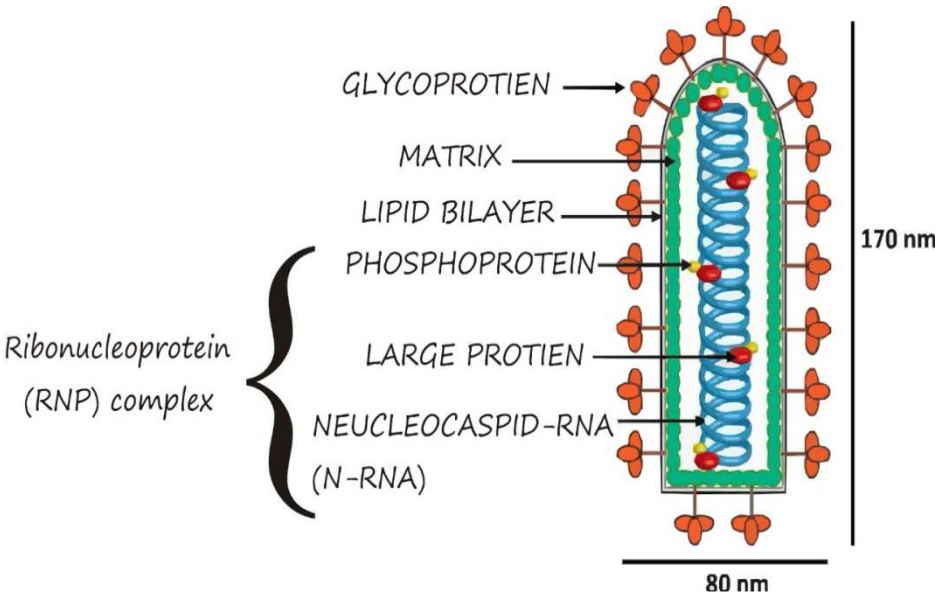

Figure 1: Structure of rabies
This figure shows the arrangement of the protein molecules in the rabies virus

IV. INCUBATION PERIOD

The highly variable incubation period for the rabies virus is 2 to 6 years and it is averagely ranges from 1 to 3 months and in the other cases it depends on the concentration of the viral substances present in the salivary glands of the rabid animal **[13]**. The efficient transmission of the virus depends on the severity of the bite of the bite by the rabid animal. The risk of acquisition of the infection is 50 times higher in the rabid animal bid than the

normal scratches(1) in some cases transplacental transmission takes place in the new born baby whose mother infected with encephalitic rabies**[14]**

V. PATHOPHYSIOLOGY OF RABIES VIRUS

Encephalitic rabies is reported to occur at the majority of the human cases hyperactive is the main sign of encephalitic rabies virus appearing as anxiety, nervousness, and mental confusions alter in with period of lucidity and preserved intelligent **[15]**. The rabies virus comes under the category of rhabadoviridae this virus consists of lyssa virus genome are single strand of negative sense RNA of 12 kilo basis(3).The viral genome serves as a template for 2 essential primary action Transcription of 5 viral mRNA. Replication to generate the full length positive sense antigenome RNA strand**[16]**.The viral genome of either negative or positive sense are always intimately encapsulated with protein while the P and L protein constitute the catalytic complex performing both transcription and replication..The order of protein genome is N > P > M > G > L the transcription generates a short leader RNA **[17]**. The L protein is involved in capping and in polyadenylation by shuttering on short stretch of seven to eight uridines

VI. THE RECEPTOR FOR THE RABIES VIRUS BINDING

The nicotinic acetylcholine receptors present in the host muscle is most probably responsible for the attachment of rabies viruses (15,11,14)**[18]**. Alphabungarotoxin is an antagonistic of the nicotinic acetylcholine receptor. This toxin substance causes neuroinvasiveness, neurotropism and neurovirulence. The RAB viral envelope is made up of the two proteins matrix (M) and glycoprotein (G) and host lipid **[19]**.

The type 1: Membrane glycoprotein consists of three potential N-glycosylation site. The endoplasmic reticulum adopts a trimeric form the glycoprotein trimer in the rab virus is responsible for the attachment of the RABV to the cell **[20].**

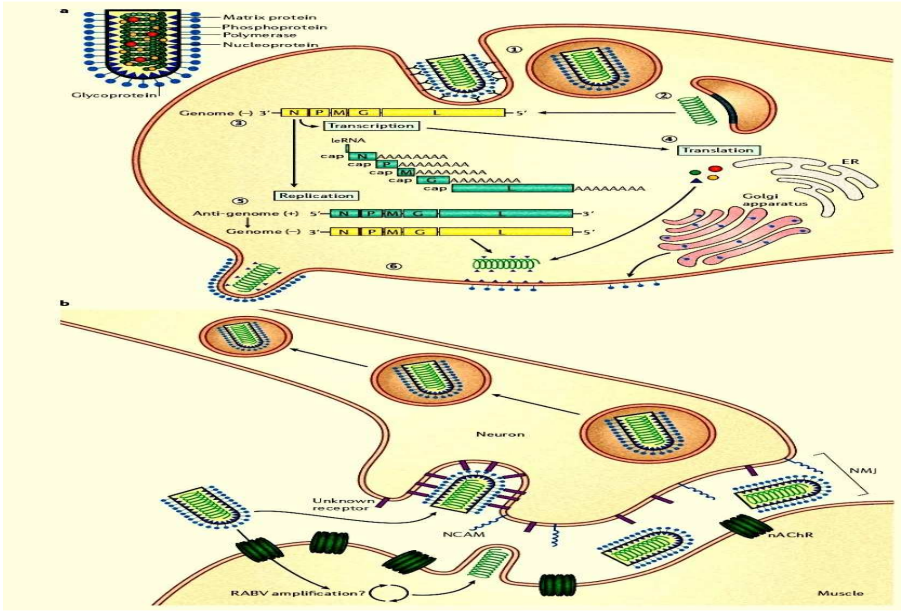

Figure 2: Neuronal transmission of RABV

This figure shows the transmission of the RABV from the axon terminal to the axon and the replication of the RABV in the axon

1. **Nicotinic Acetylcholine Receptor:** Nicotinic acetylcholine receptor is a pentameric ligand gated ion channel. This channel mediates and it modulates the interneuronal communication in the central nervous system and in the pheripheral nervous system **[21]**. The RABV'S main binding site is on the alpha x subunit of the nicotinic acetylcholine receptor binds alpha bungarotoxin. The acetylcholine produces by the muscles of adult gets accumulated at the axon terminal of the neuron by using alpha bungarotoxin autoradiography is performed this showed nicotinic acetylcholine receptor **[22].**

   The observation made by lentz et al(1982) showed the RABV binds at the location of the NACHR and the observation made by the bracciet al(1988) showed that the alpha subunit present in the muscular nicotinic acetylcholine interacts with the RAVG**[23]**. The major rabies virus genome binding site on the alpha subunit of the acetylcholine receptor is between the position 173 and 204. These following information show that the RABV binds on the acetylcholine receptor present in the muscle cell **[24]**.

2. **NCAM (Neutral Cell Adhesion Molecule):** It is also called as CD56. The NCAM is a neutral cell adhesion molecule acts a cell adhesion glycoprotein. The NCAM belongs to the immunoglobulin family **[25]**. This is involved in the neuronal migration, emotional behaviour fasciculation, synaptic plasticity and neurite outgrowth **[26]**. The NCAM has three major isoforms (NCAM-180, NCAM- 160 & NCAM-120). NCAM-120 is bound with the membrane via GPI (glycosyl phosphatidylinositol). Through transmembrane domains (TMD), NCAM-180 and NCAM-160 resides in the plasmamembrane **[27]**. This receptor is involved in the cycling of the receptor and it is also involved in the mobilization of the viral components the NCAM receptor are present in areas occupied by the nerve terminals in the post synaptic membrane NCAM -180 initiates synaptogenesis by mediating the transport of viral substance, protein binding at the site of synapse formation and in the accumulation of the synaptic organelles ie (golgibodies , vesicles ,and endoplasmic reticulum)**[28]** . The NCAM receptor acts as an antagonist to the rabies infection since the pretreatment of the RABV with the NCAM neutralises the activity of the RABV, since the soluble proteins present in the NCAM neutralises the RABV antigen. Antigen-antibody interaction takes place by the neutralising the RABV antigen and the NCAM antibody **[29]**.

VII. TRANSMISSION OF RABIES VIRUS

The RABVG enables the virus and it is transported to the central nervous system by retrograde pathway (2, . Rabies virus is transmitted by a bite of a rabid animal at the PNS site **[30]**. Then it follows is axon terminal in a retrograde path to the CNS.The most efficient route of transmission of the rabies is the transfer of RABV containing saliva from the rabid animal. Rabies transmission also occurs by the following ways.

- Tissue and organ transplant
- Handling and skinning of infected carcasses
- Inhalation of aerosolised RABV.The consumption of carcasses of the rabid animal also causes rabies infection **[31]**.

RABV in the gastrointestinal tract is due to the abrasions in the oral cavity the virus passage into the neuronal tissue. The rabies cell binds with the glycoprotein (G) and enters by the endocytosis **[32]**. This takes place in the 1st phase of the rabies virus. In the second phase the encapsulation of the virus takes place by polymerase enzymatic action then followed by the transmission of 5' end capped MRNA and the translation of the viral protein takes place the translated proteins are protein (N,P,M,G) and polymerase. After the replication process the newly synthesized anti genome acts as a template for the synthesis of additional genomic RNA. In the final step assembling of the viral genomic components takes place and then RABV virion are released starting a new round of infection RABV enter the blood stream and transport in the neuron takes place **[33]**. RABV binds with the nicotinic acetylcholine receptor which is located in the PNS this enriches the RABV at the neuromuscular junction. this indicates the nicotinic acetylcholine receptor might be used to infect the muscle cells. RABV binding also occurs in the NCAM **[34]**. The transportation of the virion takes place in the vesiclesand released in thecell body of the infected neuron

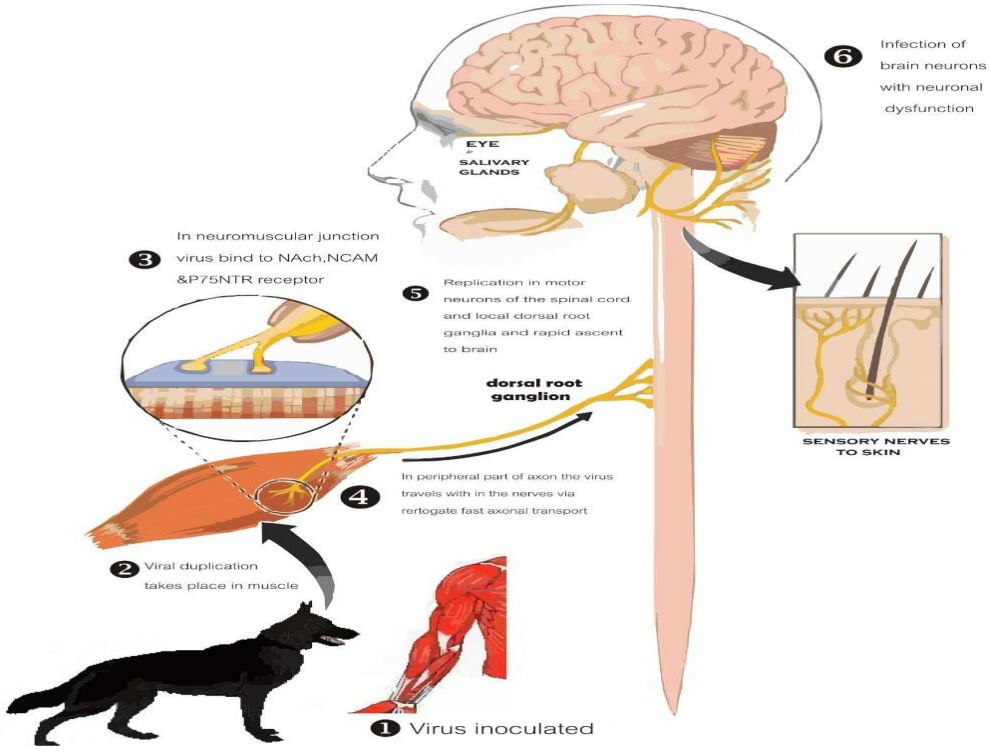

Figure 3: Transmission of the RABV from dog's saliva to neurons

Virus transmission after the dog bit into the muscle and binding with the NAch, NCAM, P75NTR receptor and neuronal transmission

VIII. PREVENTION AND CURE

All the above discussion and data had enabled disease modellingSS and prevention. In Taiwan, there is an unknown beginning of the host of the virus and they don't know that it is caused by humans or domestic animals**[35]**. And this can be compromised or prevented by the usage of using dog vaccines in the wild reservoirs and this caused major public health

concern there. At present, the discovery of non RABV lyssaviruses and the actual problem is because of unknown clinical signs and they have no difference to normal rabies infection. And in the given situation the bat population plays a major role in the spreading of lyssaviruses. And the prevention of the viruses can be done by mass vaccination of bats but this idea was never implemented if anyhow the bat spreading RAVB is very low but incorporating our knowledge with bats immunity provides protection and prevent spreading of viruses rabies has been vaccine-preventable since 1886 and we have done several advancements against rabies alive recombinant vaccine was engineered by Faber and Dietzschold and a single dose is enough but this is highly inflammatory and this made rabies vaccine more cost-effective**[36]**. Hooper and Dietzschold came up with rabies virus-neutralizing monoclonal antibody and which is joined with a freely neutralized monoclonal antibody **[37]**. This is used in phase 2 clinical trial in current times and this gives additional rabies immune globulin. And prevention can be done by combining fertility control in dogs and other vectors that make it simple and less cost-effective and prevention of rabies or eradicating it is doubtful because the other vaccine for respiratory viruses contain has rabies G glycoproteins this may cause a secondary spread of rabies and make in every one vaccinated is always have a problem related to political and economical restain treatment is fully based on symptoms only and for prevention of rabies administration of human rabies immunoglobin, steroids, and anti-thymocyte globulin has no improvement. To avoid exposure the nurses and physicians who are handling rabies patients must be vaccinated to avoid exposure to rabies **[38].**

1. **Clinical Disease:** The transfer of RABV- containing saliva from a bite from the infected animal is the most efficient route of transmission**[39]**. Other routes of transmission include: inhalation of aerosolized RABV; tissue and organ transplants; handling and skinning of infected carcasses and contamination of open wound, scratch, abrasion or mucous membrane by infected saliva or neural tissues. The efficiency of the bite transmissions depends on virus inocula and viral tissue tropism**[40]**.The incubation period after exposure in rabies in variable, typically 20 to 90 days, but ranges from a few days to a year or more. The symptoms of rabies consist of fatigue, loss of appetite, headache, insomnia, anxiety, irritability and fever lasting up to 10 days of time. The initial neurological symptoms include parenthesis, pain or irritation around the area of bite these reflects on the inflammation in the local roots ie. Dorsal roots and cranial sensory ganglia. These are categorized into Encephalitic rabies (~80%) and paralytic rabies (~20%).The burden of infection is said to revolve over the brain. There are episodes of generalized arousal ability separated by lucid periods. Autonomic dysfunction leads to hypersalivation, sweating and piloerection. This is caused by the direct attack on the autonomous nerves system entering due to the involvement of autonomic pathway of brain through hypothalamus, spinal cord, ganglia.

2. **Vaccines:** Louis Pasteur developed the first rabies vaccines to treat a human bite victim on 6th July 1885, which is considered to be one of the most effective vaccines developed against Rabies **[41]**. This method follows up with an injection to the recipient at the subcutaneous layer of the homogenate which is fully inactive in nature **[42]**.This homogenate is the RABV- infected rabbit spinal cord that has been desiccated progressively in sterile air. As vaccines produces good, it generated two main problems **[43]**. The first was consistency of inactivation and secondly, the ability to produce sufficient vaccines from rabbits to meet the demand for treatment. These vaccines also

proved to be successful but also at the same time contained high level of myelin that leads to sensitization in some recipients and in some extreme cases leads to fatal encephalitis **[44]**. Another most frequently used rabies vaccines were prepared from the brains of a sulking mice which incorporates the methods of fuenzalida and palacios. This helps in the identification of the rate of neurological reactions after the administration of nervous tissue vaccine (ntv) which is based on the idea of that brain which has not yet been myelinated with elicit less of an immunologic reaction to nervous tissue. Thentv efficacy can only be estimated. Obviously no experiments can be done on human beings. The estimated range of ntv is known from 89% to none at all **[45]**.

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