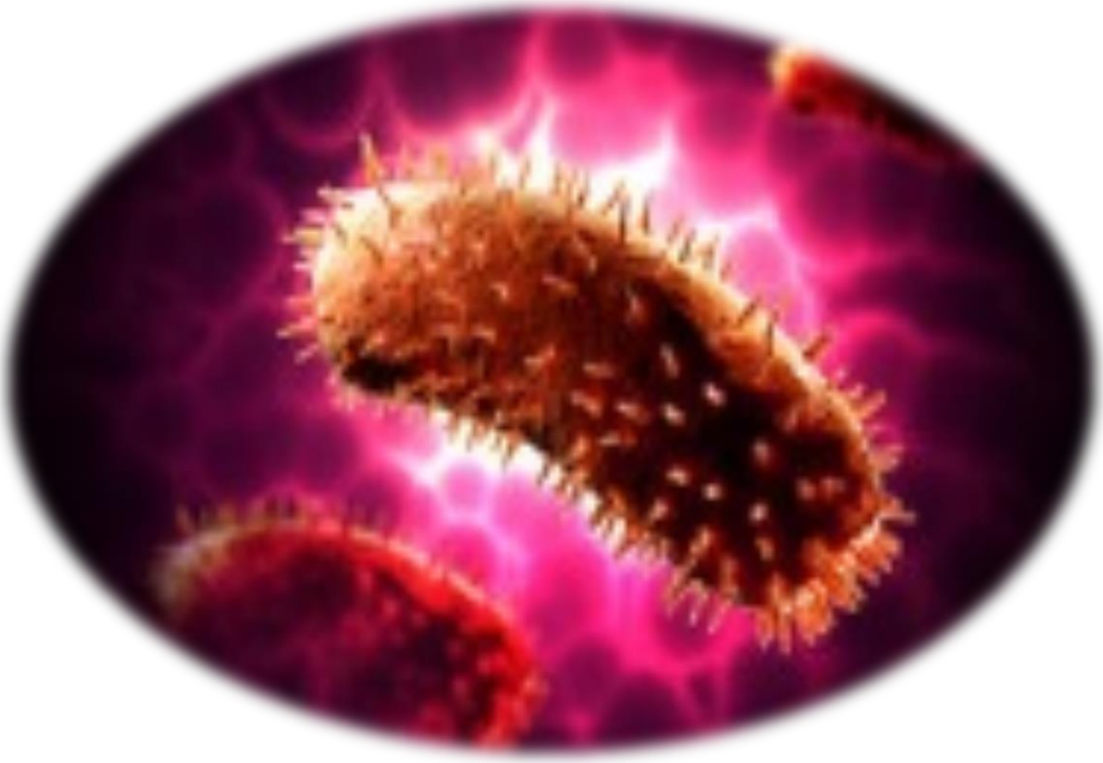

Rabies virus

" Medical virology "

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1 Introduction

1.1 History of the disease :

The word rabies is derived from the Latin word rabere , which means to be mad, to rage, or to rave , The first written description of rabies in the literature is cited in the Babylon Codex

Dog owners in the Babylonian city of Eshnunna were fined heavily for deaths caused by their dogs biting the people

Democritus, a Greek philosopher, recorded a case of canine rabies in 500 BC. In 400 BC, Aristotle wrote that ‘dogs suffer from the madness. This causes them to become very irritable and all animals they bite become diseased

In 1885, Louis Pasteur obtained his first success against rabies through postexposure vaccination , but even more than 125 years later, the disease still continues to affect mankind, especially in developing countries in Africa, Asia, and Latin America .

1.2 Introduction of the virus :

Rabies is regarded as one of the most important zoonotic diseases in the world. Commonly known as hydrophobia in man, it is a viral disease that affects the central nervous system (CNS) of humans and warm-blooded animals. Rabies is transmitted from animal to animal and from animal to man through saliva. Animal bites introduce the virus into muscle and nerve ending-rich tissues from which it penetrates into nerve cells where it replicates and progressively travels through the spinal cord to the brain , This process usually requires weeks or even months depending upon the distance from the site of the bite to the brain

The disease causes hydrophobia in man, hallucinations, aggressive behaviour, and paralysis, eventually leading to coma and death , Once the symptoms appear, rabies is nearly always fatal , Rabies has been recognised for centuries.

1.3 The distribution of this disease :

Rabies virus is known to be endemic in at least 150 countries. While in some regions, including the UK, Ireland, Sweden, Norway, Iceland, Japan, Australia, New Zealand, Singapore, most of Malaysia, Papua New Guinea, the Pacific Islands, and some islands in Indonesia have been free of the classical rabies virus for many years

but the number and size of rabies-free countries, territories, or areas are small in comparison to those of rabies-affected areas. Adequate surveillance, import

regulations, and vaccination programmes reduce the occurrence of cases of rabies in man and animals.The rabies virus is present on all continents except Antarctica. Some countries have implemented vigilant control measures and succeeded in eradicating the disease to meet the OIE requirements for rabies free status. However, in some countries, the disease remains endemic with rabies present mainly in wild animal hosts. Although the infection of domestic livestock could have economic consequences in some countries, it is the occurrence of rabies in domestic dogs posing a threat to humans that is of major concern in several developing and in-transition countries.

1.4 Epidemic :

Some countries have succeeded in controlling and even eradicating the disease by implementing vigilant control measures; however, the rabies-free status of any country, area, and population may change due to reintroduction of virus. For example, rabies was introduced in the year 2008 into the island of Bali (Indonesia), which had been free of rabies for many years. A lack of surveillance allowed the import of an unvaccinated rabid dog to Bali from Flores, a distant island where canine rabies was similarly introduced in 1997 and has since become endemic.

according to the world health organization (WHO) estimates, the number of human rabies deaths in Asia is more than 31,000 per year, of which more than 20,000 occur in India alone. India thus accounts for 36 % of the global human rabies death burden. Rabies is endemic in India except in Andaman and Nicobar a nd Lakshadweep islands, which are historically known to be rabies-free. The extent of rabies burden among animals in the country is not exactly known, but the incidence of the disease is quite high and the disease is frequently encountered in different parts of the country. The description of the outbreaks of rabies in animals during the years 1996 to 2004 reported to the World Organisation for Animal Health (OIE) . India reported 586 outbreaks among different species of animals leading to death of 2,463 animals during this period. Subsequently, 398 outbreaks of rabies in animals were reported during the period 2005 to 2011, the geographical distribution2 . Many areas of the country did not report any case during this long period of 7 years despite the endemic status of rabies there. The actual numbers, therefore,may be substantially higher, considering the possibility of underreporting due to weak rabies surveillance and inadequate reporting mechanism in the country(Garg2014).[1]

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2 Classification of the virus:

2.1. Order: *Mononegavirales*

2.2. Family: *Rhabdoviridae*

2.3. Genus: *Lyssavirus*[2]

3 Structure and Genome:

Rabies virions are bullet-shaped with 10-nm spike-like glycoprotein peplomers covering the surface.[3]

The virus is enveloped and has a single stranded, negative sense RNA genome . The RNA genome of the virus encodes five genes whose order is highly conserved. These genes codes for: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and a viral RNA polymerase (L). All rahbdoviruses have two major structural components; helical ribonucleoprotein core (RNP) and surrounding envelops. The two proteins, P and L are associated with RNP. The glycoprotein forms approximately 400 trimeric spikes, which are tightly arranged on the surface of the virus . The virus nucleoprotein (N) plays critical role in replication and transcription. Both viral transcription and replication are reduced, if the nucleoprotein is not phosphorylated.[4]

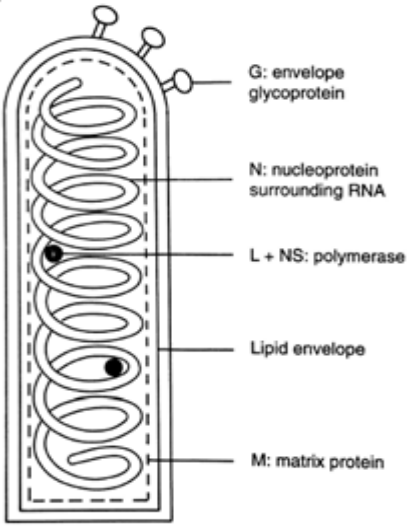

Figure 2- Virion structure of rabies virus.

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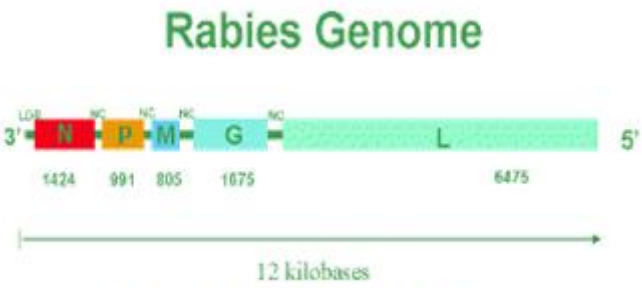

Figure 1 - Rhabdovirus genome

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4 Proteins (Virulence Factors):

The virus has only five proteins:

G (Surface) Protein:

This is the surface glycoprotein spike and exists as trimers. There are about 1200 G proteins (400 trimers) per virus particle. It is a transmembrane protein with an N-terminal signal sequence. The G protein binds to cellular receptors and is the target of neutralizing antibodies. There are three sugar chains that are N-glycosidically attached. Penetration of the virus into the cytoplasm takes place in the endocytic

pathway and not at the plasma membrane. This is because the G protein trimer undergoes a change in conformation at pH 6.1 which stabilizes the trimer and probably allows a hydrophobic region of the molecule to become exposed and to embed in the membrane of the cell to be infected.

M (matrix) protein:

This is a peripheral membrane protein (originally M stood for membrane) that appears to line the inner surface of the viral membrane, though this remains somewhat controversial. It may act as a bridge between the membrane or G protein and the nucleocapsid.

Nucleocapsid:

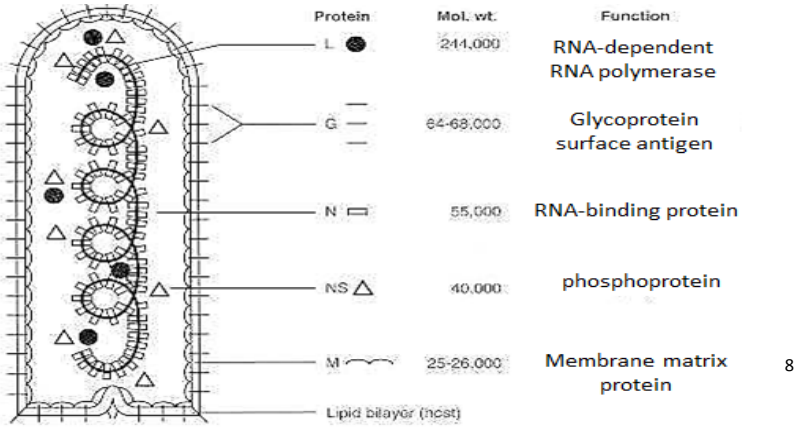
This is the infectious ribonucleoprotein core of the virus. It is a helical structure that lies within the membrane. In negative stain electron micrographs, such as seen in figure 1, the nucleocapsid has a striated appearance.

N (Nucleoprotein) protein:

This is the major structural protein and covers the RNA genome. It protects the genome from nucleases and holds it in a conformation that allows transcription

L (Large) protein and NS (nonstructural, otherwise known as P (phospho)):

protein together form the RNA-dependent RNA polymerase or transcriptase. The L protein has a molecular weight of 240 kiloDaltons and its gene takes up 60% of the genome .[7]



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5 Transmission :

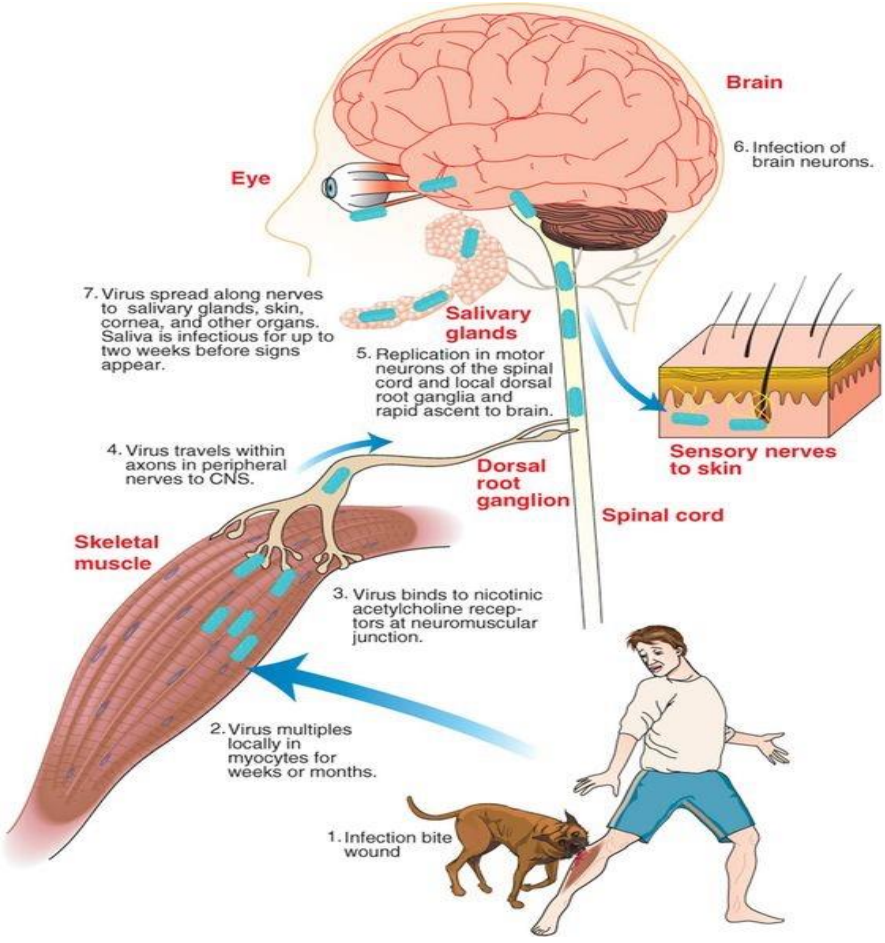
5.1 The Sources Of Rabies Virus :

Rabies virus has a wide host range. All warm-blooded animals and humans can be infected. Susceptibility varies among mammalian species ranging form very high (Fox,Coyotes,Wolves) to low (Opossums) intermediate (Skunks,Raccoons,Bat) .

large number of the virus could be funded in nervous system , saliva , urine , blood of the infected animals. the recovery of rabies virus is vary rare except in some bats where it become weirdly adapted to the saliva glands in these cases they are carrying it and can infect human and other animals.(Brooks et al 2013)[9]

5.2 How Does Rabies Virus Infect People:

The transmission of Rabies virus could be with different ways commonly by bitten of infected animal but it could be also be contact of the virus with mucous membrane or open wound can spread the virus throw the body and cause infection



.(Bhatia & Ichhpujani 2008)[10]

6 Penetration and the Target Organ :

6.1 The Process After Infection :

Rabies Virus multiplies in muscle or connective tissue site of inoculation then goes to peripheral nerves to reach central nerve system then spreads through peripheral nerves to the salivary glands and other tissues.Susceptibility to infection and the incubation period may depend on the host's age, genetic background, and immune status, the viral strain involved, the amount of inoculum, the severity of lacerations, and the distance the virus has to travel from its point of entry to the central nervous system. ere is a higher attack rate and shorter incubation period in per- sons bitten on the face or head; the lowest mortality occurs in those bitten on the legs.(Bhatia & Ichhpujani 2008)[10]

7 Replication Cycle (the main site):

Rabies virus life cycle in the cell . It take place entirely in the cytoplasm of the infected cells.Virus enters the cell following attachment through coated pits (viropexis) or via cell surface receptors , mediated by the viral glycoprotein (G) fusing with the cellular membrane (endocytosis) . After internalization , the viral G mediates low pH - dependent fusion with the endosomal membrane and the virus is uncoated , releasing the helical nucleocapsid (NC) of the ribonucleoprotein (RNP) core . The five structural genes (N , P , M , G , and L) of the genome RNA (vRNA) in the NC are transcribed into five positive (+) strand monocistronic messenger (m) RNAs and a full - length + strand (anti - genome) replicative intermediate RNA (cRNA) , which serves as the template for replication of progeny genome (-strand) vRNA The proteins (N , P , M , and L) are synthesized from their respective mRNAs on membrane free ribosomes in the cytoplasm and the G is synthesized the

G mRNA on membrane- bound ribosomes (rough endoplasmic reticulum) .[11]

7.1 Attachment :

Surface protein of the Rabies virus (glyocoprotein spikes G) inter act with the cell surface receptors.(Brooks et al 2013)[9]

7.2 Penetration :

The Rabies virus will be indulged to the cell by endosome first it make a grouve then the virus will be in vesicle inside the cell.(Brooks et al 2013)[9]

7.3 Uncoating :

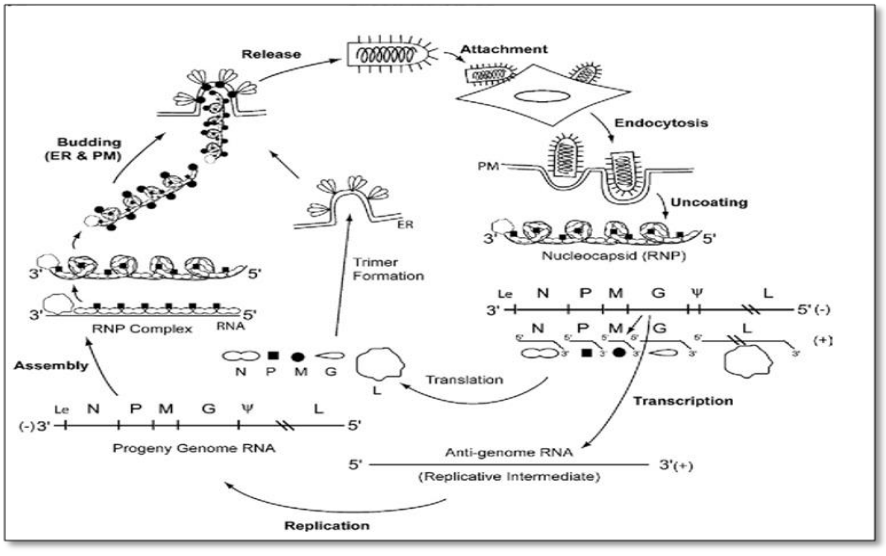
The rabies virus genome will be released in the cytoplasm of the host cell in this step the core of the virus will flout in the cytoplasm after the endosomal membrane fuses then the nucleocapsid will be uncoted.

7.4 Transcription and translation :

1. Transcription of (-) strand occurs after entry and is mediated by virion packaged transcriptase.
2. (+) strand RNA's are produced; proteins are synthesized.
3. Full-length (-) strand RNA's are produced and packaged into newly forming virions.
4. Transcription and translation take place entirely in the cytoplasm infected cells.(Bhatia & Ichhpujani 2008)[10]

8 Assembly and Egression :

During the assembly process, the N-P-L complex encapsulates negative-stranded genomic RNA to form the RNP core, and the M protein forms a capsule, or matrix,



around the RNP. The RNP-M complex migrates to an area of the plasma membrane containing glycoprotein inserts, and the M-protein initiates coiling. The M-RNP complex binds with the glycoprotein, and the completed virus buds from the plasma membrane. Within the central nervous system (CNS), there is preferential viral budding from plasma membranes. Conversely, virus in the salivary glands buds primarily from the cell membrane into the acinar lumen. Viral budding into the salivary gland and virus-induced aggressive biting-behavior in the host animal maximize chances of viral infection of a new host.

Assembly and budding of RABV is thought to occur in the following stepwise manner: (i) The nucleocapsid core forms as the N protein interacts with newly synthesized genomic RNA. The polymerization of the N protein onto the RNA backbone is facilitated by the release of N protein from N–P dimers in the cytoplasm. The RABV M protein is also able to recognize and interact with the newly forming RNP structures in the cytoplasm. (ii) Simultaneously with RNP formation, the RABV G protein localizes to the plasma membrane, the site of virion formation and budding. (iii) RABV M protein accumulates on the cytoplasmic side of G-enriched microdomains on the plasma membrane as the RNPs condense into tightly coiled structures by interacting with M protein. (iv) The microdomains containing high levels of G protein along with the continued condensation of M-RNP structures are thought to facilitate outward membrane curvature and eventual virion egress. (v) Last, the PPEY motif of RABV M engages host Nedd4 E3 ligase and likely recruits the cellular vps machinery to the site of RABV budding to facilitate the final step of virus–cell separation.(Jackson 2011)[12]

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9 Symptoms of Rabies :

The initial onset of rabies begins with flu-like symptoms, including:

- fever
- muscle weakness
- tingling

You may also feel burning at the bite site.

Other symptoms include:

- insomnia
- confusion
- agitation
- hallucinations
- excess salivation
- problems swallowing
- fear of water

Infected people slowly become paralyzed, will eventually slip into a coma, and die.[13]

10 Diagnosis and Cytopathic effect :

10.1 Diagnosis in animals :

A diagnosis of rabies can be made after detection of rabies virus from any part of the affected brain, but in order to rule out rabies, the test must include tissue from at least two locations in the brain, preferably the brain stem and cerebellum.

The test requires that the animal be euthanized. The test itself takes about 2 hours, but it takes time to remove the brain samples from an animal suspected of having rabies and to ship these samples to a state public health or veterinary diagnostic laboratory for diagnosis.

10.2 Diagnosis in humans :

Several tests are necessary to diagnose rabies ante-mortem (before death) in humans; no single test is sufficient. Tests are performed on samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.[14]

10.3 cytopathic effect :

Effects on the nervous system:

When an unvaccinated animal or human is bitten by an animal carrying rabies virus in its saliva, the virus remains in the region of the bite site for variable periods of time, sometimes even replicating within the non-nerve local tissue cells (connective tissues, muscle cells etc.),before migrating to the nerve endings in the region and entering them. The time taken to go from the bite site into the nerve endings can be days to months (in cats and dogs the range is usually between 2 weeks and 6 months, in humans the range can be more than a year). No signs of rabies disease will be seen within this period (it is called the rabies incubation period)

The nerve endings that supply the muscles and skin of the limbs and face (allowing the animal to move its muscles or feel sensations such as heat, pain, cold and pressure)are like the ends of long fingers. The rabies virus migrates from the nerve-ending entry point (near the bite site), up the axon and into the nerve cell itself, where it replicates (according to Greene CE, this migration up an axon goes at speeds of 10-400mm/day). Replication of the rabies virus in the nerve cell results in injury or death of that cell and, as a result, the animal may display signs of nerve

injury as an early manifestation of the rabies infection. This nerve damage can present as paralysis of a limb or a facial region if the nerve ending invaded had the job of supplying electrical messages to the muscles in order to create movement. Animals bitten on the leg may drag the limb that was bitten and animals bitten on the face might lose the ability to blink or to swallow. This is how the condition 'paralytic rabies', otherwise known as 'dumb rabies.

Rabies viruses enter axon endings (nerve endings) located in the spinal cord and then travel up them to their nerve cell bodies (where the nucleus and cytoplasm is). These nerve cell bodies might be located in the brain or higher up in the spinal cord(towards the animal's head). In the nerve cell, the process of virus replication and cell damage is repeated. More viruses erupt and invade more axons and the process continues. Eventually, through this process of replication and axonal entry and migration, the rabies viruses reach the brain. The brain contains hundreds of closely-associated brain cells and millions of very short axons, in which to gain entry to those cells. Consequently, once the rabies virus enters the brain, the process of virus invasion and replication really takes off in a big way. It is here, with millions of brain cells being invaded and destroyed, that the symptoms of full-blown rabies really become apparent.[15]

11 Control the virus and Prevention :

Rabies is a preventable disease. There are some simple measures you can take to help keep you from catching rabies:

- Get a rabies vaccination before traveling to developing countries, working closely with animals, or working in a lab handling the rabies virus.
- Vaccinate your pets.
- Keep your pets from roaming outside.
- Report stray animals to animal control.
- Avoid contact with wild animals.
- Prevent bats from entering living spaces or other structures near your home.

You should report any signs of an infected animal to your local animal control or health departments.[13]

12 Treatment :

Doctors will treat your wound by washing it for at least 15 minutes with soap and water.[13]

12.1 Rabies vaccine:

Rabies vaccine is given to people at high risk of rabies to protect them if they are exposed. It can also prevent the disease if it is given to a person after they have been

exposed.

Preventive vaccination (no exposure):

People at high risk of exposure to rabies, such as veterinarians, animal handlers,

*** The vaccine should also be considered for:**

People whose activities bring them into frequent contact with rabies virus or with possibly rabid animals.

International travelers who are likely to come in contact with animals in parts of the world where rabies is common.

The pre-exposure schedule for rabies vaccination is 3 doses, given at the following times:

* Dose 1: As appropriate

* Dose 2: 7 days after Dose 1

* Dose 3: 21 days or 28 days after Dose 1

For laboratory workers and others who may be repeatedly exposed to rabies virus, periodic testing for immunity is recommended, and booster doses should be given as needed.

12.2 Vaccination after an exposure:

A person who is exposed and has never been vaccinated against rabies should get 4 doses of rabies vaccine - one dose right away, and additional doses on the 3rd, 7th, and 14th days. They should also get another shot called Rabies Immune Globulin the same time as the first dose.

A person who has been previously vaccinated should get 2 doses of rabies vaccine - one right away and another on the 3rd day. Rabies Immune Globulin is not needed.[16]

13 Host Immune Defense :

Rabies virus enters the nervous system via a motor neuron through the neuromuscular junction, or via a sensory nerve through nerve spindles. It then travels from one neuron to the next, along the spinal cord to the brain.

After injection of rabies virus intramuscularly or after nasal instillation, the standard local (for example in the lymph nodes of the injected hind limb) and systemic (in spleen) immune responses develop. In the lymph node, blood and spleen, rabies virus infection triggers the appearance of activated lymphocytes (CD69+) secreting

cytokines, and expressing collapsin response mediator protein 2 (CRMP2), a marker of cell polarisation and migration . Peripheral injection of rabies virus in mice triggers the production of circulating neutralizing antibodies. The intensity of the immune response in the periphery after injection of an acute rabies virus strain is not different from that triggered by an attenuated strain of rabies virus. Thus, the immunosubversive strategy developed by rabies virus to escape the host immune response does not take place in the periphery.[17]

14 Genetics (Gene Mutation) :

There are various ways viral mutations can occur, for example through copying mistakes during gene replication or damage from ultraviolet light.

"If a rabies virus can mutate fast enough, it could cause infection within an hour or a few hours.[18]

We investigated a virus-neutralizing conformational epitope of the rabies virus glycoprotein (G) that is recognized by an anti-G monoclonal antibody (mAb; #1-46-12) and shared by most of the laboratory strains of the virus. To investigate the epitope structure, we isolated escape mutants from the HEP-Flury virus (wild-type; wt) after repeated passages in culture in the presence of the mAb. Immunofluorescence studies indicated that the mutants could be classified into two groups; the Group I lacked the epitope, while Group II preserved the epitope. The latter was dominant under the passage conditions, since Group I disappeared during the continuous passages. G proteins showed different electrophoretic mobilities; G protein of Group I migrated at the same rate as wt G protein, while that of Group II migrated at a slower rate, which was shown to be due to acquisition of an additional oligosaccharide side chain. Nucleotide sequencing of the G gene strongly suggested that amino acid substitutions at Thr-36 by Pro and Ser-39 by Thr of the G protein are responsible for the escape mutations of Groups I and II, respectively. The latter is a unique mutation of the rabies virus that allows the G protein to be glycosylated additionally at Asn-37, a potential glycosylation site that is not glycosylated in the parent virus, in preserving the epitope-positive conformation. These results suggest that to keep the 1-46-12 epitope structure is of greater survival advantage for the virus to escape the neutralization than to destroy it, which could be achieved by acquiring an additional oligosaccharide chain at Asn-37.[19]

15 Recent discoveries :

1. First international collaborative study to evaluate rabies antibody detection method for use in monitoring the effectiveness of oral vaccination programmes in fox and raccoon dog in Europe .

the use of alternative methods such as the enzyme-linked immunosorbent assay (ELISA) has been proposed to improve reliability of serological results obtained on wildlife samples. We undertook an international collaborative study to determine if the commercial BioPro ELISA Rabies Ab kit is a reliable and reproducible tool for rabies serological testing. Our results reveal that the overall specificity evaluated on naive samples reached 96.7%, and the coefficients of concordance obtained for fox and raccoon dog samples were 97.2% and 97.5%, respectively. The overall agreement values obtained for the four marketed oral vaccines used in Europe were all equal to or greater than 95%. The coefficients of concordance obtained by laboratories ranged from 87.2% to 100%. The results of this collaborative study show good robustness and reproducibility of the BioPro ELISA Rabies Ab kit.[20]

2. Veterinary Rabies Vaccine :

To present a mini review of other methods for its production and technological development to suppress serum in rabies vaccine for use in veterinary medicine.[21]

3. Ineffectiveness of rabies vaccination alone for post-exposure protection against rabies infection in animal models

To develop more efficacious vaccine against rabies. In our evaluation of a novel PIKA rabies vaccine, we used multiple animal models (beagles, golden hamsters and Kunming mice) to mimic post-exposure scenarios. All animals were challenged with wild-type rabies virus, followed by vaccination with either rabies vaccines commercially available or PIKA rabies vaccines. As 100% of animals survived after administration of traditional rabies vaccines and rabies immunoglobulin, 80% of animals survived with rabies immunoglobulin alone. Strikingly, animals receiving traditional rabies vaccines alone showed extremely low survival rates, indicating insignificant benefit for exposed animals ($p > 0.05$, compared to unvaccinated control groups). To the contrary, 40–80% of animals receiving the experimental PIKA rabies vaccines were protected ($p < 0.05$, compared to unvaccinated control groups). If the above results are fully confirmed, we may conclude that currently as high as 99% of post-exposure patients who are seeking protection against rabies, but only receiving rabies vaccination, could be meaningless.[22]

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