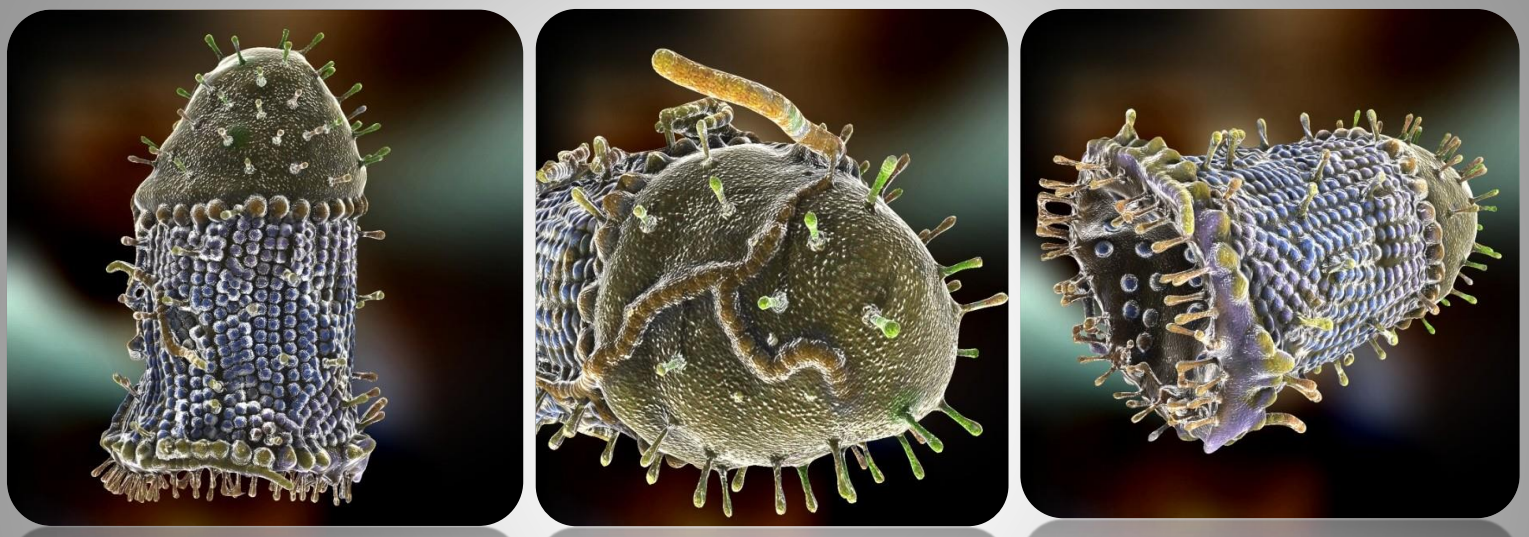
The Rabies Virus



Contents

The Classification

Order: Mononegavirales

Family: Rhabdoviridae

Genera: Lyssavirus" rabies virus group"

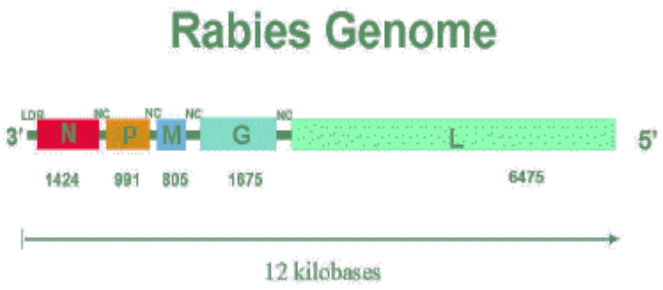
structute

- Rhabdoviruses are approximately 180 nm long and 75 nm wide.
- All rhabdoviruses have two major structural components:

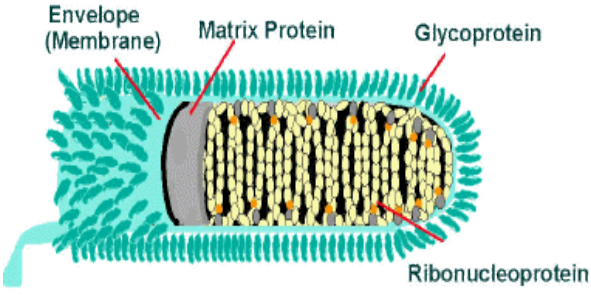
  (a helical ribonucleoprotein core (RNP)+ and a surrounding envelope).
- Rabies is an RNA virus. The genome is single-stranded, antisense, nonsegmented, RNA of approximately 12 kb. There is a leader-sequence (LDR) of approximately 50 nucleotides, followed by N, P, M, G, and L genes.

The genome encodes 5proteins

1. nucleoprotein (N) .
2. phosphoprotein (P) .
3. matrix protein (M) .
4. glycoprotein (G) .
5. polymerase (L) : (transcriptase)



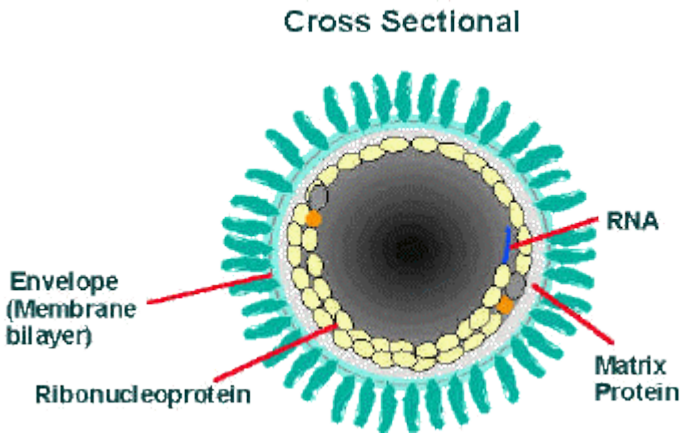
- polymerase (L) : Two other viral proteins, the phospoprotein and the large protein (L-protein or polymerase) are associated with the RNP.



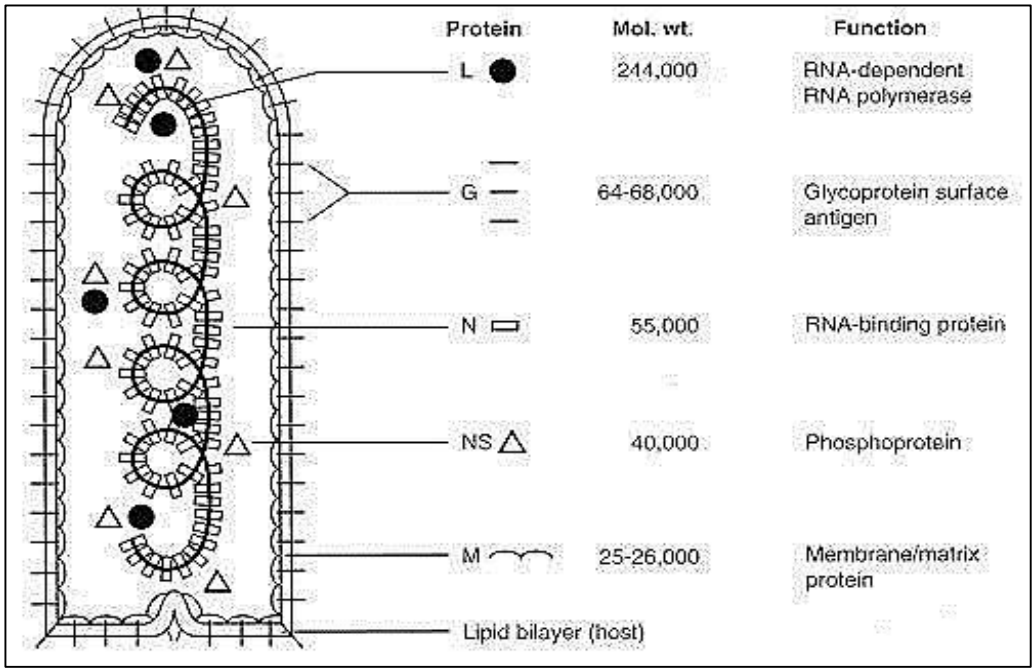
- The glycoprotein (G): forms approximately 400 trimetric spikes which are tightly arranged on the surface of the virus.
- Matrix protein (M) : he M protein is associated both with the envelope and the RNP and may be the central protein of rhabdovirus assembly.

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

The ribonucleoprotein is composed of RNA encased in nucleoprotein - (), phosphorylated or phosphoprotein -Illistration of virus, and polymerase -virus.



envelope membrane bilayer, M protein, and tightly coiled encased genomic RNA.

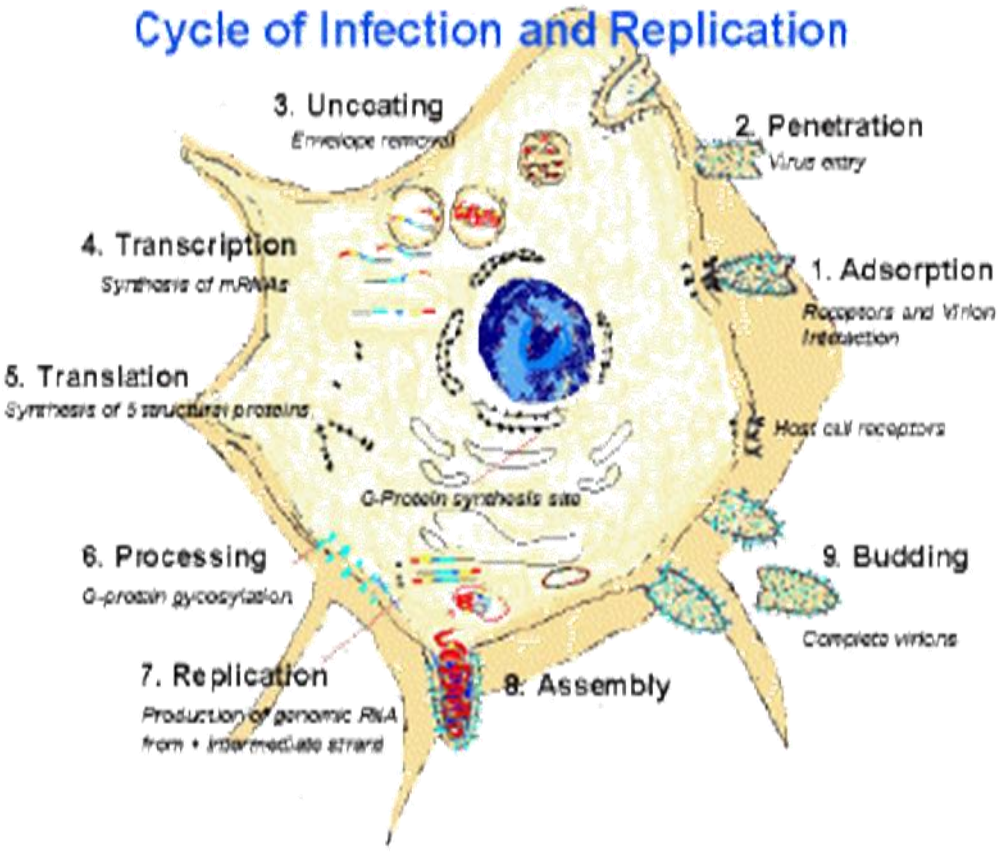


The virus genome encodes five proteins associated with either the ribonucleoprotein (RNP) complex or the viral envelope :

- The L (transcriptase)
- N (nucleoprotein), and NS (transcriptase-associated) proteins comprise the RNP complex, together with the viral RNA. These aggregate in the cytoplasm of virus-infected neurons and compose Negri bodies, the characteristic histopathologic finding of rabies virus infection.
- The M (matrix) and G (glycoprotein) proteins are associated with the lipid envelope. The G protein forms the protrusions that cover the outer surface of the virion envelope and is the only rabies virus protein known to induce virus-neutralizing antibody.

Replication of Rabies Virus:

When a human or animal is injected with infected saliva, the rabies virus replicates at the site of inoculation. All transcription and replication events take place in the cytoplasm inside a specialized “virus factory“, the Negri body the rabies virus recognize the host cell via acetylcholine receptors , The fusion of the rabies virus envelope to the host cell membrane (adsorption) initiates the infection process. The interaction of the G protein and specific cell surface receptors may be involved. After adsorption, the virus penetrates the host cell and enters the cytoplasm by pinocytosis (via clathrin-coated pits). Both processes, receptor binding and membrane fusion are catalyzed by the glycoprotein G which plays a critical role in pathogenesis (mutant virus without G proteins cannot propagate). The virions aggregate in the large endosomes (cytoplasmic vesicles). Inside the endosome, the low pH value induces the membrane fusion process, thus enabling the viral RNP genome to reach the cytosol (uncoating).Because lyssaviruses have a linear single-negative-stranded ribonucleic acid (RNA) genome, messenger RNAs (mRNAs) must be transcribed to permit virus replication. A viral-encoded polymerase (L gene) transcribes the genomic strand of rabies RNA into leader RNA and five capped and polyadenylated mRNAs, which are translated into proteins.



1: Adsorption (receptors and virion interation).

2: Penetration (virus entry).

3: Uncoating (envelope removal).

4. Transcription (synthesis of mRNAs).

5. Translation (Synthesis of structural proteins).

6. Processing (G-protein gycosylation).

7. Replication (production of genomic RNA from intermediate strand.

8. Assembly. 9: Budding (complete virions).

Translation, which involves the synthesis of the N, P, M, G and L proteins, occurs on free ribosomes in the cytoplasm. Although G protein synthesis is initiated on free ribosomes, completion of synthesis and glycosylation (processing of the glycoprotein), occurs in the endoplasmic reticulum (ER) and Golgi apparatus. The intracellular ratio of leader RNA to N protein regulates the switch from transcription to replication. When this switch is activated, replication of the viral genome begins. The first step in viral replication is synthesis of full-length copies (positive strands) of the viral genome. When the switch to replication occurs, RNA transcription becomes "non-stop" and stop codons are ignored. The viral polymerase enters a single site on the 3’ end of the genome, and proceeds to synthesize full-length copies of the genome. These positive strands of rabies RNA serve as templates for synthesis of full-length negative strands of the viral genome.

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.

Disease and pathogenicity

- Rabies is a viral disease of warm-blooded animals and humans, caused by virus, which is present in the saliva of infected animals, transmitted through the bite of a rabid animal, and usually manifested by acute fatal encephalomyelitis.
- Rabies is a dangerous disease due to its transmissibility to humans and its fatal outcome.
- All mammals can carry rabies. However, the following species are more commonly infected:

  Dogs / bats / raccoons / foxes / jackals / cats / mongooses / monkeys.

How can I tell if an animal has rabies?

In general, any animal behaving abnormally should be suspected of having rabies, and should be avoided.

In animals, rabies may exhibit two forms, dumb or furious rabies.

In dumb or paralytic rabies :

- Some animals may show signs of depression and will try to hide in isolated places
- Wild animals may lose their fear of humans and appear unusually friendly; and/or

- Animals may show signs of partial paralysis such as abnormal facial expressions, drooping head, sagging jaw, or paralyzed hind limbs.

In furious or irritable rabies :

- Animals may show signs of extreme excitement and aggression;
- Animals may gnaw and bite their own limbs;
- Animals may attack stationary objects or other animals; and
- Periods of furious rabies usually alternate with periods of depression.

Rabid animals may exhibit any combination of the above two forms or they may exhibit no clinical symptoms at all.

Rabies transmission:

The saliva becomes filled with infectious virus particles which can be passed on to another animal through the following routes:

1. biting: the infected animal bites another creature and the virus-filled saliva gets pushed into the open wounds made.
2. infection of an open wound: rabies filled saliva that contaminates a pre-exit in open wound or scratch can lead to infection.
3. infection of the mouth, nose or eyes
4. scratches: some animals (e.g. cats and bats) lick their claws as part of their grooming procedures. Infectious viral particles can pass from the saliva-coated claws into a human or animal should they be scratched by that rabid animal.
5. aerosolized saliva: it is uncommon to be exposed to aerosolized saliva, but in poorly ventilated, enclosed and overcrowded areas (regions with lots of humidity and airborne respiratory and salivary aerosols), it is possible for humans and other animals to inhale aerosolised, microscopic saliva particles carrying

infectious virions. This can lead to infection - the virus crosses the mucous membrane linings of the lungs.

6. ingestion of secretion : occasionally, consumption of infected secretions can leadto rabies transmission.
7. human-to-human transmission- transmission from cornea and organ transplants, The only well-documented cases of rabies caused by human-to-human transmission

Clinical Features

•Five general stages of rabies are recognized in humans:

1. Incubation.(The incubation period in rabies, usually 30 to 90 days but ranging from as few as 5 days to longer than 2 years after initial exposure)
2. prodrome.
3. Acute neurologic period.
4. Coma.
5. Death.

1. The incubation period

The incubation period is the time it takes for symptoms to develop after a person is infected with the virus. The incubation period for rabies is usually 2 to 12 weeks, although it can be as short as four days. It would be highly unusual for the incubation period to last for more than a year.

The incubation period depends on a number of factors, including:

1- the severity of the wound

2- the location of the bite

3- the susceptibility of the person to infection. People who are immunocompromised will most likely be more susceptible to rabies.

The shorter the incubation period is infection your brain, . For example, a bite to your face, head or neck has a shorter incubation period than a bite to your arm or leg.

The length of the incubation period is important because it is the only period in which treatment can be successful.

2. <u>Prodrome</u>

The prodromal stage begins when the virus moves from the periphery to dorsal-root ganglia (causing neuropathic pain) and to the CNS. These developments mark the end of the incubation period, and most patients die within the next 2 weeks.

At this stage there, Symptoms are vague, variable, and non specific

3. <u>Acute neurological phase</u>

Are divided into two type:

Classic rabies - Non-classic rabies

1- <u>Classic rabies</u>

During the acute neurological phase, objective signs of nervous-system dysfunction begin. Mental dysfunction can be seen in patients with encephalitic rabies as well as some with paralytic forms, but to a much greater degree in the encephalitic group.

Two-thirds of patients with classic rabies have an encephalitic form, and the remainder present with paralysis.

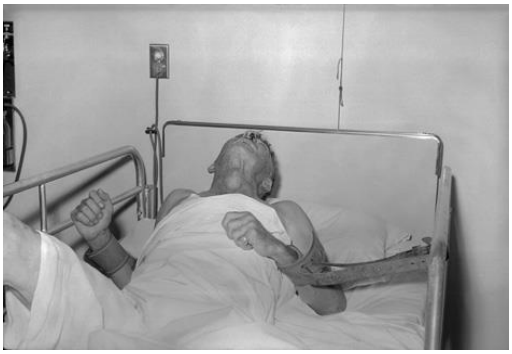
Most patients with the encephalitic form die within 7 days (average 5 days) of onset, and the average survival period is about 2 weeks in paralytic cases.

Initial symptoms.

The initial symptoms of rabies are often vague, and it can be easy to mistake them for other less serious types of infection. **They include:**

a high temperature of 38ºC (100.4ºF) or above / chills / fatigue (extreme tiredness) problems sleeping / lack of appetite / headache / irritability / anxiety / sore throat / vomiting

Around half of people will also experience pain and a tingling sensation at the site of the infection.



Advanced symptoms

Initial symptoms of rabies last for two to 10 days before more severe symptoms start to develop.

There are two types of advanced rabies:

- furious rabies, which accounts for four out of five cases
- dumb or paralytic rabies, which accounts for the remainder of cases

Furious rabies

Furious rabies is characterised by episodes of increasingly odd and hyperactive behaviour, separated by periods of relative calm. During these episodes a person may have some or all of the following signs and symptoms:

- aggressive behaviour, such as thrashing out or biting
- agitation
- hallucinations – seeing or hearing things that are not real
- delusions – believing things that are obviously untrue
- excessive production of saliva

- high temperature (fever)
- excessive sweating
- the hair on their skin stands up
- a sustained erection (in men)

People with furious rabies will also develop hydrophobia (a fear of water).

This initially begins as a pain in the throat or difficulty swallowing. . There will also be fear of bright light (photophobia) and fear of breezes (aerophobia).

A few days after these symptoms develop, the affected person will fall into a coma and die, usually as a result of heart or lung failure.

Dumb or paralytic rabies

- Dumb rabies, sometimes called paralytic rabies, is characterised by muscle weakness, loss of sensation and paralysis (inability to move one or more muscles). This usually begins in the hands and feet before spreading throughout the body.
- Hydrophobia is unusual in cases of dumb rabies, although muscles may go into spasm. With dumb rabies will fall into a coma and eventually die from heart or lung failure.

2- Non-classic rabies

Patients with bat-related rabies to have clinical features substantially different from those of dog-related cases. In addition to neuropathic pain, which is much more common, there are reports of radicular pain, objective sensory , and choreiform movements of the bitten limb during the prodromal phase.

Both focal brainstem signs and myoclonus are common.

Other patients have been described as having ataxia, vertigo, or Horner's syndrome.Convulsive and non-convulsive seizures and hallucinations are frequent.

4-Coma

Inspiratory spasms may be useful in diagnosis at this stage.

However, they are difficult to detect in paralytic rabies

because of weakness a prime cause of death, in almost all cases. Hematemesis is seen in 30–60% of patients 6–12 h before death.

5- Death.

Epidemiology

Rabies in Asia

- Most of the developing countries in Asia are the victims of rabies
- over 30,000 people die every year due to rabies in Asia
- One Asian dies every 15 minutes
- More than 3 billion people in developing countries in Asia are exposed to dog rabies
- 15% are likely to be the children under 15 years
- India / Cambodia / Magnolia /China /Nepal / Srilanka /Pakistan / Bangladesh

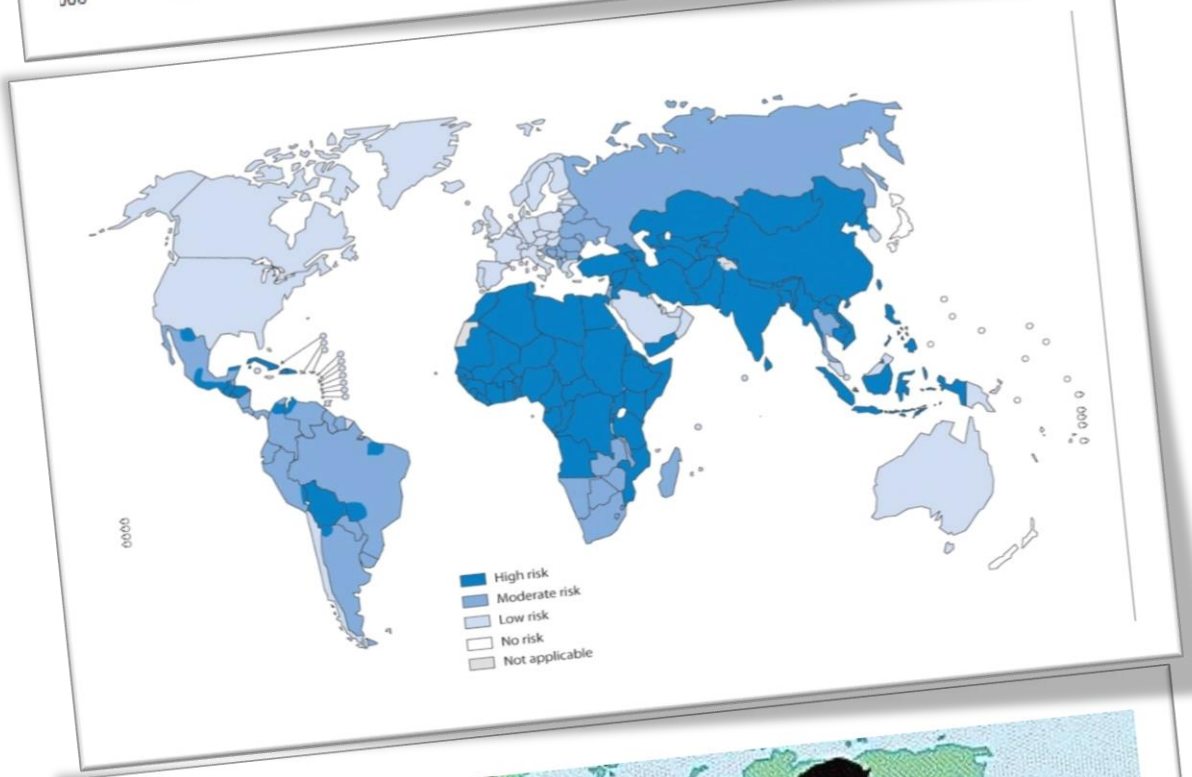
Rabies in Africa

- Rabies causes at least 24,000 deaths per year in Africa.
- The high death rates reported in poor rural communities and children
- An unconfirmed epidemic of in 1901. The existence of rabies in 1928
- Other southern African countries like; Angola, Namibia, Mozambique and Zimbabwe

Rabies in Europe

- Persons who emigrated from North Africa to France .This travel pattern also creates a pathway for rabies reintroduction to France.
- Rabies is still present in Europe, but the human rabies has been disappeared from many European countries
- The disappearance of rabies was probably due to enforced policy of animal vaccination

eath	y/sex	exposure	Animal species	Incubation time	onset and death	received rabies PE
970	3/M	Niger	Cat	10 d	9 d	Unknown
973	10/M	Gabon	Dog	11 mo or 15 d	20 d	Unknown
976	5/M	Gabon	Dog	45 d	1 mo	Unknown
976	18/M	Algeria	Dog	Unknown	23 d	1
976	28/M	Morocco	Unknown	Unknown	1 mo	Unknown
976	10/M	Algeria	Dog	1 mo	18 d	Unknown
976	2/M	Gabon	Dog	18 d	1 d	5
977	4/M	Morocco	Dog	1 mo	2 d	25
977	57/F	Egypt	Dog	2 mo	10 d	12
979	36/M	Egypt	Human (cornea transplant)	1 mo	15 d	128
980	4/M	Tunisia	Dog	2.5 mo	3 d	66
982	40/M	Senegal	Dog	122 d	30 d	Unknown
990	28/M	Mexico	Dog	47 d	10 d	1
992	3/M	Algeria	Dog	1 mo	3 wk	143
994	46/M	Mali	Dog	3 mo	11 d	36
996	3/M	Madagascar	Dog	2 mo	6 d	290
996	60/M	Algeria	Dog	2 mo	5 d	45
996	71/M	Algeria	Dog	40 d	3 d	35
997	50/F	India	Dog	12 d	56 d	36
003	3/M	Gabon	Dog	>2 mo	10 d	142
008	42/M	France (French	Bat	Unknown	16 d	90



Laboratory Diagnosis

The diagnosis of human rabies is usually suggested by epidemiologic and clinical findings and confirmed in the laboratory. The diagnosis is not difficult if there is a history of animal bites exposure and if a full spectrum of symptoms and signs has appeared.

Early in the course of illness, rabies can mimic numerous infectious and noninfectious diseases. Many other encephalitides, such as those caused by herpesviruses and arboviruses, resemble rabies.

Laboratory Diagnosis

The detection of rabies antigen, antibody, viral RNA, or the isolation of virus establishes a diagnosis of rabies. Because any individual test may not be positive in a patient with rabies,

Specimens: Serial serum specimens for detection of rabies antibodies, saliva specimens for culture of virus, and skin biopsies for direct immunofluorescence testing for virus antigen are sometimes necessary, especially when rabies is strongly suspected.

Two distinct forms of rabies furious / paralytic are recognized in humans.

Diagnosis of the classical furious (encephalitic) form, which constitutes about 80% of human rabies cases, is based on its distinctive clinical signs and symptoms and rarely poses diagnostic difficulties. However, laboratory assistance may be required in some cases wherein characteristic clinical features like aerophobia or hydrophobia are lacking. In clinical practice, the paralytic or atypical forms, which constitute about 20% of human rabies cases, pose a diagnostic dilemma.

- Early diagnosis can obviate the need for unnecessary treatment and medical tests.
- Also help in prognostication, institution of barrier nursing.

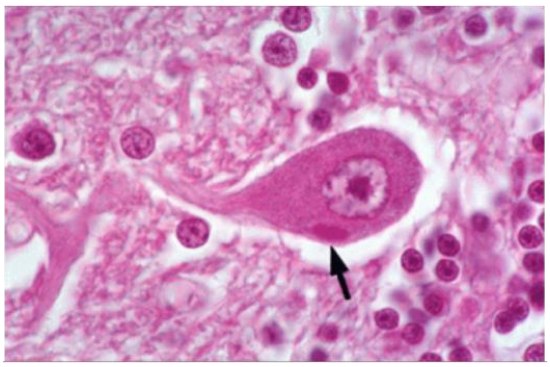
- Timely administration of pre- or post-exposure prophylactic vaccination to family members of the patient and the treating medical and nursing staff.
- Case closure and grief counselling with family members.

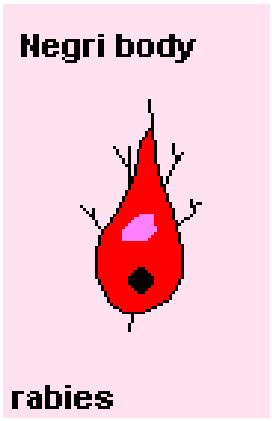
Conventional Diagnostic Tests for Rabies:

Advantages and Limitations

Direct Microscopy: Histological Identification of Characteristic Cell Lesions

"Negri bodies": Infected neuronal cells reveal aggregates of viral particles "Negri bodies" which are intra cytoplasmic inclusion bodies specific to rabies encephalitis. Demonstrated by histological tests (Seller's Technique) on smears taken from various areas of the brain. Negri bodies vary in size from as small as 3 μm to as large as 30 μm and are generally circular or oval and deeply eosinophilic with characteristic basophilic granules, often arranged in the form of a rosette, within the eosinophilic matrix





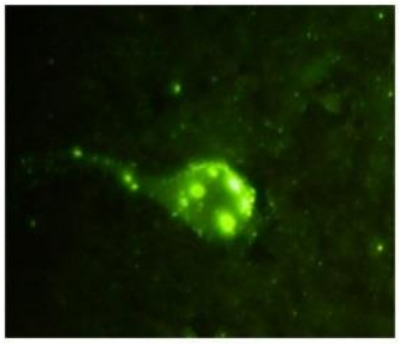
Demonstration of Viral Antigen

Fluorescent Antibody Technique (FAT) Developed by Goldwasser and Kissling in 1957

The most widely used test for postmortem rabies diagnosis is the fluorescent antibody test (FAT). It involves demonstration of the rabies virus nucleoprotein antigen (N) in fresh brain smears of a suspected rabies case by using immunofluorescence technique . It can also be used to confirm the

presence of rabies antigen in cell culture or in brain tissue of mice that have been inoculated for diagnosis.

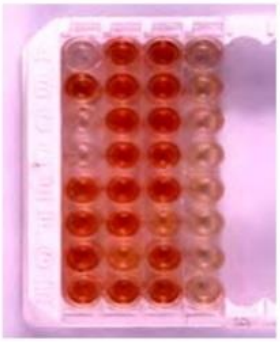
The specificity and sensitivity is 99% in an experienced laboratory and results are available within a few hours



Fluorescent antibody technique (FAT) on human brain smear positive for rabies

Reliable results are obtained only when fresh brain tissue is used ;. Partially decomposed brains are not suitable for this test as it is very difficult to differentiate specific fluorescence due to N antigen from nonspecific fluorescence which may result from bacterial contamination.

Rapid Rabies Enzyme Immunodiagnosis (RREID)



The rabies N antigen can also be detected by applying immunohistochemical techniques as well as enzyme immunoassays by ELISA ..

The advantage is that partial decomposition of the brain will not affect the test result. A limitation of the test is requirement of brain tissue, which precludes its use in ante mortem diagnosis.

Diagnosis of rabies by the Rapid Rabies Enzyme Immunodiagnosis (RREID) technique.

Note the dark brown colouration obtained with rabies positive brains in comparison to negative brains which appear colourless.

Virus Isolation : Virus isolation is required for confirmatory diagnosis, especially when FAT gives an uncertain result . Two techniques can be employed for this purpose: the mice inoculation technique (MIT) and rapid tissue culture infection test (RTCT).

Mouse Inoculation Test (MIT)

Three-to-ten mice, 3-4 weeks old (12–14 g), or a litter of 2-day-old newborn mice, are inoculated with virus . The inoculated mice are observed daily for 28 days; they develop typical signs and symptoms of rabies any time after 5–7 days depending on the incubation period.

Symptoms:

- ruffling of hair
- hunch back
- dragging hindlimbs followed by paralysis of hind
- forelimbs

Further confirmation of the diagnosis can be made by extracting the brain of the diseased mouse and subjecting this to FAT .

The disadvantage of MIT is the long interval before a diagnosis can be made since the inoculated mice need to be kept under observation for 28 days as some wild viruses may have a very long incubation period.

The advantages of MIT are that when the test is positive, a large amount of virus can be isolated from a single mouse brain for strain identification purposes and that it can be easily and practicably applied .

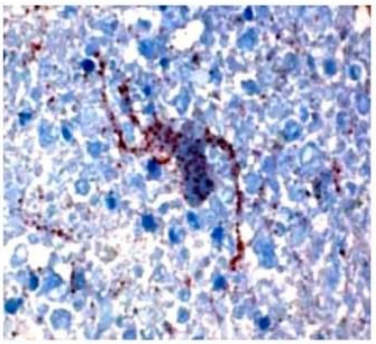
Demonstration of Antibodies

The demonstration of antibody in the serum in the absence of a history of vaccination for rabies or in CSF offers indirect evidence of rabies infection. Interpretation of test results may be difficult since the host immune response may vary among individuals ; but may assist in diagnosis of paralytic rabies, where the survival is relatively longer.

Direct Rapid Immunohistochemical Test (dRIT)

Test is based on detecting rabies N protein in suspected brain smears fixed in buffered formalin using a cocktail of highly concentrated and antibody to N protein followed by addition of streptavidin peroxidase and substrate colouring reagent The rabies N antigens

If present, are found as brownish red clusters within the neuron, along the axons and scattered all over the brain smears .



The Direct Rapid Immunohistochemical Test (dRIT) technique done on a human brain positive for rabies. Note the presence of brownish .

Immunochromatographic Techniques

Another recently described method for the detection of rabies virus antigen from postmortem samples is the rapid immunodiagnostic test (RIDT)..There are other antigen detection assays ..

Other Techniques:

- Nucleic Acid Detection Techniques
- Reverse Transcriptase PCR (RT-PCR)
- Real-Time PCR
- Demonstration of Antibodies :Enzyme-linked immunosorbent assay (ELISA)
- Proteomics and Metabolomics
- *Indirect Rapid Immunohistochemistry Test (IRIT)*
- *Rapid Tissue Culture Infection Test (RTCT)*

Treating rabies

The treatment given for rabies will depend on whether you have started to show signs or symptoms.

If you show no signs or symptoms and it is suspected you may be infected, a course of treatment called post-exposure prophylaxis (PEP) is used. This can usually prevent a rabies infection from becoming established and producing symptoms.

If you have symptoms of rabies, treatment will usually focus on making you as comfortable as possible. This is because rabies is almost always fatal when it reaches this stage.

These two types of treatment are described in more detail below.

Post-exposure prophylaxis

Post-exposure prophylaxis consists of three elements:

- cleaning the wound
- administering rabies immunoglobulin – a special preparation of antibodies
- administering a course of the rabies vaccine

Cleaning the wound

Immediately after being bitten, you should:

- wash the wound thoroughly under a running tap
- use antiseptic or alcohol to clean the wound and apply ethanol, tincture or aqueous solution of iodine, if available
- leave the wound open – use a simple dressing but do not try to stitch it, because this could expose your nerve endings to the rabies virus

- go to the nearest hospital or medical centre and explain you have been bitten

If you think your eye may have been infected with the saliva of an animal, you should wash it thoroughly with clean water and seek medical help.

Rabies immunoglobulin

If there is a high risk you are infected with rabies, you should be given an injection of rabies immunoglobulin. This should help protect you against the virus and prevent it travelling to your nervous system.

The immunoglobulin works by providing ready-made antibodies designed to neutralise the rabies virus and prevent it from spreading.

Aside from some temporary soreness at the site of the injection, rabies immunoglobulin does not usually cause any side effects.

Vaccination

The rabies vaccine should be given in every case of suspected exposure to rabies. The length of your course of vaccinations will depend on whether you have previously been vaccinated.

If you have never been vaccinated, you should receive five doses of the vaccine. The first dose is given at the beginning of the treatment, followed by four further doses, which are given three, seven, 14 and 30 days after the start of treatment.

If you have previously been vaccinated, you should receive two doses of the vaccine. The first dose is given at the start of your treatment, followed by a second dose three to seven days later. The doses are given by injection into the shoulder muscle.

A common side effect of the rabies vaccine is redness, swelling and pain at the site of the injection that occurs 24 to 48 hours after the injection has been given.

Choice of vaccine

There are three types of rabies vaccine:

- human diploid cell vaccine (HDCV), which is created by using samples of human cells
- purified chick embryo cell rabies vaccine (PCEC), which is created by using samples of chicken embryos
- nerve tissue vaccine, which is created using samples of nerves taken from animal brains

The World Health Organization (WHO) recommends that only HDCV or PCEC should be used. This is because there are safety concerns over the nerve tissue vaccine. Researchers have found this type of vaccine has a one in a 650 chance of causing serious complications that can result in permanent disability, such as muscle paralysis.

A small number of countries have not followed the WHO recommendation and still use the nerve tissue vaccine. They include Mongolia, Myanmar (Burma) and Pakistan.

In many developing countries, the HDCV or PCEC vaccine may only be available if you are willing to pay for private treatment.

If you are offered the nerve tissue vaccine, it is recommended you refuse and ask for one of the alternative vaccines.

Supportive treatment

If a person who is infected with rabies is not treated and they have developed symptoms, rabies is said to be established.

In this situation, there is almost nothing that can be done apart from keeping them comfortable. This is usually done by using powerful tranquilisers and sedatives to keep them free from physical pain and emotional upset.

To date, there have been no reported cases of human-to-human transmission of rabies. However, it is theoretically possible, so anyone who has been in close contact with someone who has a rabies infection may be advised to have post-exposure prophylaxis as a precaution.

In very rare cases, established rabies infections have been treated using a technique called the Milwaukee Protocol.

The Milwaukee Protocol

Until recently, all cases of established rabies infection were thought fatal.

However, a technique called the Milwaukee Protocol was attempted in 2004 on a patient with established rabies, and it saved their life. It involves inducing a coma so the person's brain is protected while their immune system tackles the infection.

Since then, the lives of five more people with rabies, none of whom had post-exposure prophylaxis treatment, have been saved using this technique.

However, this technique has only been used about 35 times overall and currently has a low success rate.

It is therefore still considered to be highly experimental and is not widely used.

Prevention:

To help prevent rabies

- Vaccinate your pet. Rabies vaccines are available for dogs, cats and farm animals
- Don't let pets roam
- Don't approach stray animals. Animals with rabies might be aggressive and vicious, or tired and weak

References

- The classification and nomenclature of virusesby International Committee on Taxonomy of Viruses ,Accepted January 9, 1976
- Charles E. Rupprecht , Medical Microbiology. 4th edition,
- http://www.cdc.gov/rabiesandkids/virus.html
- http://www.ncbi.nlm.nih.gov/books/NBK8618/
- http://www.cdc.gov/rabies/transmission/virus.html
- http://osp.mans.edu.eg/elsawalhy/Inf-Dis/Rabies.htm#nature
- http://www.health.gov.on.ca/english/public/program/pubhealth/rabies/qa/rabies_animals_qa.html
- http://www.pet-informed-veterinary-advice-online.com/rabies.html#rabies-catch
- http://www.health.gov.on.ca/english/public/program/pubhealth/rabies/qa/rabies_qa.html
- http://www.nhs.uk/Conditions/Rabies/Pages/Symptoms.aspx
- http://rabies.emedtv.com/rabies/rabies-symptoms.html
- http://www.sciencedirect.com/science/article/pii/S1474442202000418
- http://www.nhs.uk/Conditions/Rabies/Pages/Causes.aspx
- http://www.ncbi.nlm.nih.gov/books/NBK8618/
- http://www.virologyj.com/content/9/1/50#sec4
- http://www.medscape.org/viewarticle/753884_2
- http://www.medscape.com/viewarticle/771913_2
- http://www.infectionlandscapes.org/2013/05/rabies.html
- http://www.virologyj.com/content/9/1/50#sec4
- http://www.medscape.org/viewarticle/753884_2
- http://www.medscape.com/viewarticle/771913_2
- http://www.infectionlandscapes.org/2013/05/rabies.html
- http://www.nlm.nih.gov/medlineplus/rabies.html