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THE SIGNIFICANCE OF MODERN DIAGNOSTIC METHODS OF RABIES VIRUS IN MEDICINE

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Abstract:
In the analysis of these literatures, the pathogenesis of the rabies virus in humans in recent years (2012-2022), ways of transmission, modern diagnostic methods, widely used vaccinations, importance of serological, molecular biological, immunological methods used in treatment and diagnosis, their possibilities and advantages are presented. . For example, the Rapid Fluorescent Focus Inhibition Test (RFFIT), ELISA, viral RNA - RT-PCR, immunofluorescent test (dFAT), mouse inoculation test (MIT), as well as many clinical trials conducted on patients have shown the effectiveness of several vaccines and pharmacological agents. for example, Rabisin™, Recombitek®C6/CV, Recombitek®C8, SPBN GASGAS, SAD L16, and several immune boosters are among them

Keywords: *molecular-biological, PCR, RT-PCR, (CDV), adenovirus (CAV), parvovirus (CPV), parainfluenza virus (CPiV), immunofluorescent test (dFAT), mouse inoculation test (MIT) and polymerase chain reaction (PCR), Recombitek®C6/CV, Recombitek®C8, Rabisin™*

INTRODUCTION

Rabies is a zoonotic disease with a fatality rate of almost 100%. Approximately 59,000 people die of rabies every year worldwide, with the vast majority of deaths oc- curring in the developing countries of Asia and Africa, and 50% of these deaths were children under 15 years of age . In some economically developed countries, the occur- rence of rabies has been effectively controlled through the vaccination of dogs. In less developed areas, the preven- tion and control of rabies are hampered because of the low levels of medical treatment available, insufficient re- serves of vaccines and immunoglobulins, and the lack of attention from the public, resulting in a large number of reported cases of rabies . The causative agent of ra- bies, the rabies virus (RABV), is highly neurotropic and all mammals are susceptible to the virus. The transmission of RABV is mainly through bites or scratches from infected animals, usually dogs. In recent years, the RABV has also been transmitted by bats, foxes, and other wild animals in some countries, such as the United States and Russia(Chenjuan Shi).

However, RABV continues to be enzootic in large parts of the world, such as in Asia and Africa, where it causes an estimated 35,172 cases and 21,476 human deaths yearly (WHO).(Bas B. Oude Munnink).

Nevertheless, rabies is preventable through post-exposure prophylaxis (PEP), which has shown a good efficacy . However, this prophylaxis costs 40 United States dollars, when the average daily allowance in Africa and Asia is 1–2 dollars per person, making it unaffordable for most population at risk. The persistence of rabies in Africa is mainly fuelled by the vicious cycle of the lack of accurate epidemiological data, the negligence of the populations and decision-makers, the

lack of public information and sensitization on the risk of rabies, and the geographic and financial barriers to access rabies vaccines(Jocelyne Noel Sowe Wobessi).

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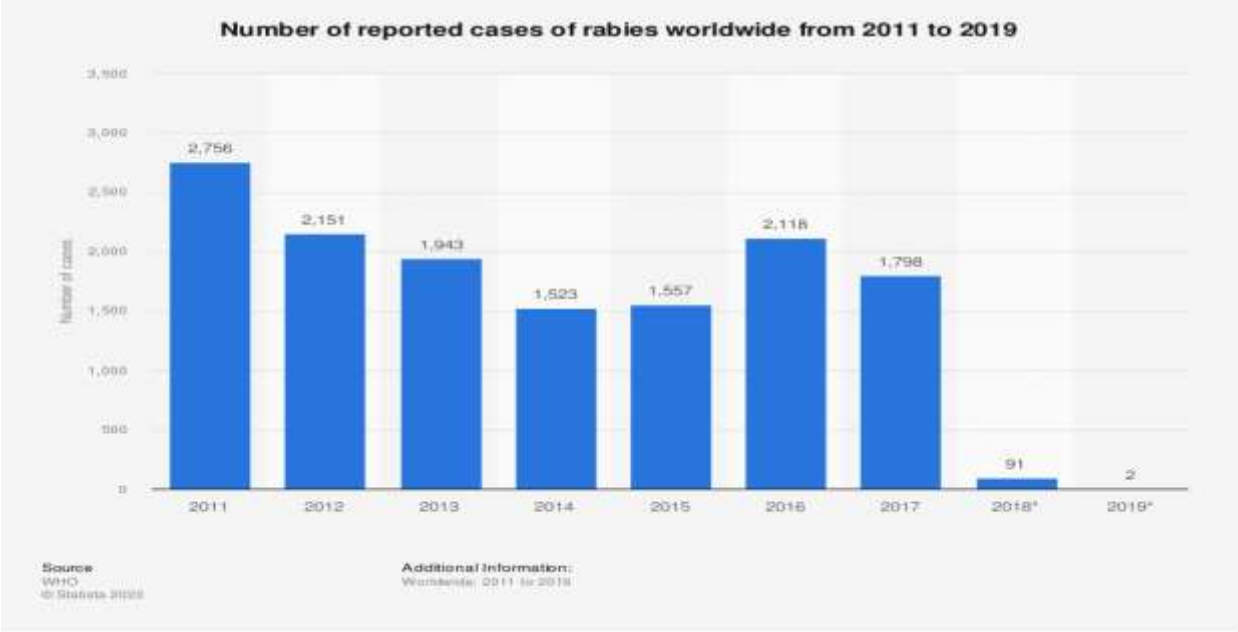
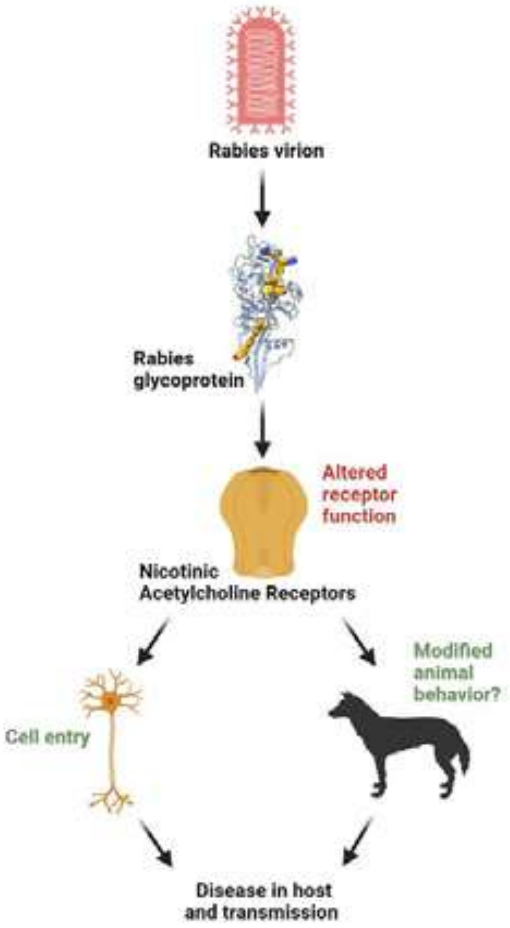


Etiology

1. Etiology of the RABV

RABV belongs to the Rhabdovirus family, Lyssavirus genus, and is the prototypic lyssavirus. The lyssaviruses are classified into phylogroups based on genetic and antigenic data . All the members of the Lyssavirus genus are highly neurotropic, and can cause fatal encephalitis, similar to rabies. Theoretically, all mammalian species are susceptible to lyssavirus infec- tions. Most infections caused by lyssaviruses other than RABV have been found in dogs, cats, civets, bats, and other animals(Chenjuan Shi) Apoptosis can be detected during
late stages of the infection . Nevertheless, how viral infection and neurotropism translate to disease is still unclear . The molecular mechanisms
leading to these extensive behavior changes, including aggression, hyper sociability, hydrophobia, and hypermobility, are uncertain, although newer reports have started to unveil some possible mechanisms(Marianne Lian).
Dogs are the main reservoir for human
rabies (Hampson et al., 2015). RABV is commonly subdivided into six phylogenetic clades,
namely the Africa 2, Africa 3, Arctic-related, Asian, Cosmopolitan, and Indian subcontinent clades. In Nepal, both the Arctic-related as well as the Indian subcontinent RABV clade are present (Pant et al., 2013), while the Cosmopolitan RABV clade currently circulates in the Arabic Peninsula (Horton et al., 2015; Troupin et al., 2016). Recently, two RABV infections were diagnosed in Qatar in Nepalese migrant workers.(Bas B. Oude Munnink). Documented host species of RABV include domestic animals, but also wild-living carnivores comprising foxes and raccoon dogs in Europe , foxes in the Middle East, raccoon dogs and ferret-badgers in Asia, skunks , foxes, coyotes and mongooses in the Americas, African civet and mongooses in Africa . Owned dogs are the principal hosts involved in the transmission of RABV to human in more than 99% of cases through bites . Rabies is almost always fatal once clinical disease develops.(Jocelyne Noel Sowe Wobessi)



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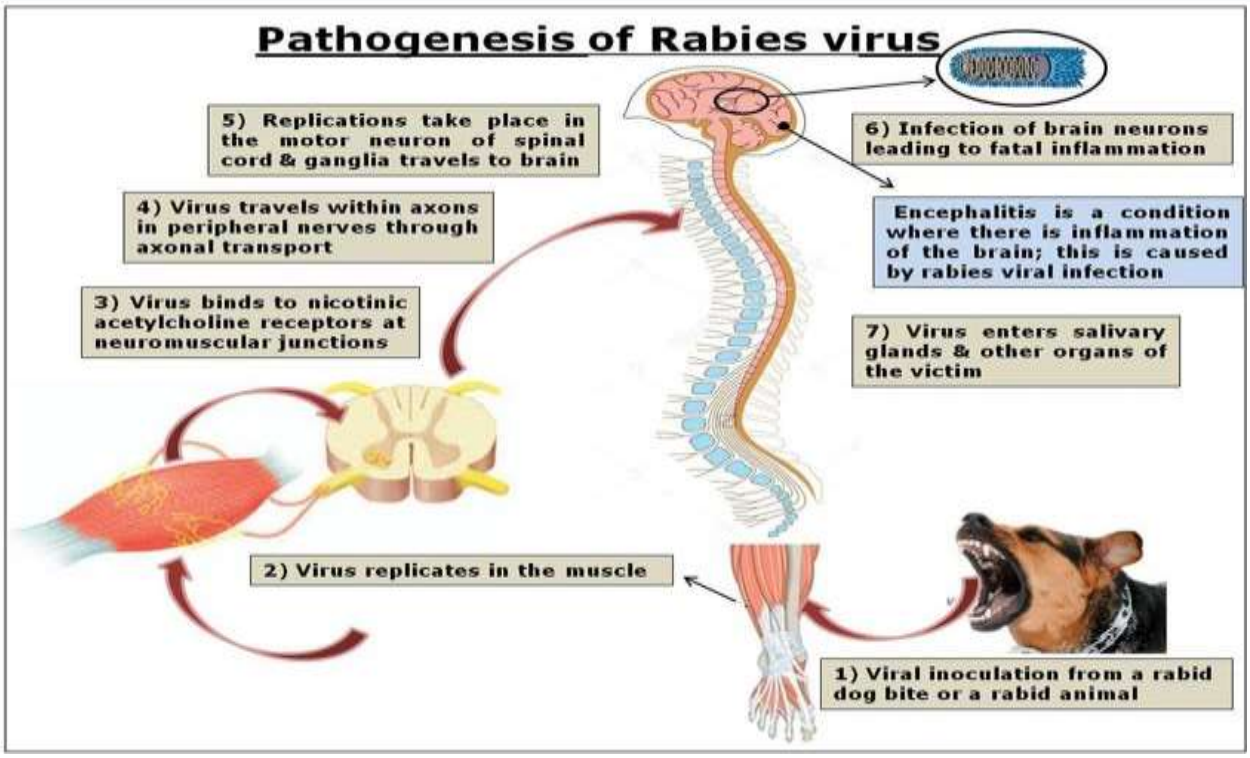
Clinics

Rabies has a case fatality rate approaching 100% once clinical signs occur owing to a lack of satisfactory treatment options once the virus has entered the central nervous system (CNS).(Marianne Lian). The incubation period of the disease is long and depends on localization of the bite and the dose of the virus that entered the tissue. When bitten in the face, head, neck, upper limbs, the most short incubation period (7-10 days). With the most common bites to the lower extremities the average incubation period for rabies is 1-3 month. Sometimes it can exceed 1-2 years. Registered cases of rabies with an incubation period of 10, 13 and even 19.5 years.(kin). Penetrating into tissues after a bite, the virus through the supercapsid protein G binds to n-acetylcholine receptors on membranes neurons and neuromuscular connections. There are two possible pathogenic variant of the infection. In one of them, the virus penetrates into muscle cells and multiplies locally at the site bite. In this case, it can stay in the muscle for a long time. tissue (up to 2 months). In another variant, the virus binds to transport proteins in the axoplasm of peripheral nerves (dynein, neurotropin) and retrograde along axons
is transported to the CNS to the bodies of neurons of the spinal and brain brain. The rate of retroaxonal transport here is 50- 100 mm/day, which shortens the incubation period. .(kin). After entering the CNS, the virus actively multiplies in spinal cord, brainstem neurons, hippocampus, subcortical ganglia, thalamus, cerebellum. Newly formed viruses are centrifugally distributed throughout the body with damage to skeletal muscles, heart, blood vessels, salivary glands,
retina of the eye, all internal organs.(Generalov.I.I)

Pathogenesis

The prodromal period of the disease lasts several days. There is a headache, vomiting, fever increases, there are sensory disturbances at the entrance gate of infection. At the height of the disease, there are two main forms clinical manifestations of rabies - violent and paralytic. With a violent form, symptoms of motor and mental arousal. Patients feel fear spasms of the swallowing and respiratory muscles appear at the sight of water (hydrophobia); attacks are repeated under the influence of bright 161 light (photophobia), loud sound (acousticophobia), flow action air (aerophobia). Aggressiveness, riot, intensifies sweating and salivation (hypersalivation). The fever reaches critical values (over 41-42o WITH). The infection ends lethal in 2-8 days. In the paralytic form, initially there is a local paralysis affecting the affected limb. Progression disease leads to generalized paralysis. Death of patients occurs within 30 days from the onset of clinical manifestations.(Generalov.I.I)



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Diagnostic Methods

Since the rabies virus belongs to group III pathogens risk, work with it must be carried out in compliance with appropriate biosecurity measures in specialized laboratories. A definitive diagnosis of rabies can be made only with the help of methods of laboratory diagnostics with virus identification. Laboratory methods are used to confirm the diagnosis. post-mortem (post-mortal) and intravital diagnostics rabies. The material for the study are biopsy specimens of the brain fabrics; also examine biopsies of the skin of the back of the neck (back of the head) containing hair follicles with nerve endings (follicles).

The most widely used detection of antigen rabies virus in brain tissue by immune fluorescence (gold standard" diagnostics). The technique of light microscopy with the detection of Babesh-Negri bodies in the cytoplasm of affected neurons is inferior in terms of diagnostic accuracy of immune fluorescence. It is also used to detect viral antigens in tissues. ELISA; viral RNA - RT-PCR. Rabies virus can be detected on cell cultures already within 1-2 days using RIF, ELISA or PCR.

AG of the virus is detected in the reaction of immune fluorescence; viral RNA is detected by PCR. Saliva, lacrimal fluid and cerebrospinal fluid are used for intracerebral infection laboratory animals (mice, rabbits) or for cultivation of the virus in cell culture. For serodiagnosis, it is possible to use ELISA and other reactions with the detection of antiviral antibodies in serum patients or their cerebrospinal fluid (in the later stages of the disease). However, in most cases, serodiagnosis is used for assessing the level of immunity during vaccination Human rabies is a fatal disease which kills hundreds of people per year. Early diagnosis is important in the therapy, direct immunofluorescent test (dFAT), mouse inoculation test (MIT) and polymerase chain reaction (PCR) are used for routine diagnosis, but with a considerable false negative rate . The metagenomics next-generation sequencing (mNGS) as a novel option in diagnosis of rabies were seldom reported. In this case, In this case, we describe the diagnostic method (using mNGS) and the therapy of a patient who developed rabies syndrome after dog(Lan Pin, Xie Lutao, Lai Linjie). The evaluation of RVNA requires reliable serological methods to help ascertain immune status and determine efficacy of pre- or postexposure vaccination. There are several different assays that are used to measure immune responses to rabies vaccination, including calculating RVNA titers via cell-based methods, such as the Rapid Fluorescent Focus Inhibition Test (RFFIT), the fluorescence readout based antibody virus neutralization test, the simplified fluorescence inhibition microtest and pseudotype virus micro-neutralization assays, or enzymelinked immunosorbent assay (ELISA) based methods, such as the indirect fluorescence antibody test, the immunoperoxidase inhibition assay, and the counter immunoelectrophoresis test (World Health Organisation/Department of Control of Neglected Tropical Diseases, 2018).

Treatment

Anti-rabies drugs are used for immunization immunoglobulins of equine and human origin. Also Various types of drugs are being developed for the treatment of rabies.

humanized monoclonal antiviral antibodies. There have been numerous attempts at medical treatment and prevention of rabies. For some drugs their anti-rabies activity has been established, at least in in vitro conditions (eg, rifampicin). In 2004, the first successful attempt was made in the United States treatment of rabies that developed in a patient after being bitten by a bat mice; while anti-rabies vaccination was not carried out. The patient was on sedatives and anticonvulsants introduced into an artificial coma with simultaneous appointment antiviral agents (ribavirin, amantadine). At the end treatment and long-term rehabilitation of the victim

her recovery was confirmed with the elimination of the rabies virus from organism.

At the place of execution, this treatment regimen received called the Milwaukee (or Wisconsin) Protocol. However further results of this treatment regimen are very contradictory. 5 cases of recovery registered in the treatment of 43 people. In general, the development of an effective drug therapy for rabies remains a matter of the future.(Generalov.I.I). Vaccines Recombitek®C8: freeze-dried vaccine containing a recombinant canarypox expressing glycoproteins HA and F of the canine distemper virus (CDV) and 3 live attenuated viruses (Canine Adenovirus 2 -CAV2, Canine Parvovirus - CPV and Canine Parainfluenza Virus - CPiV) + liquid vaccine containing 4 inactivated Leptospira serovars (Icterohaemorrhagiae – Li; Canicola – Lc; Grippotyphosa – Lg; Pomona – Lp). Recombitek®C6/CV: freeze-dried vaccine containing a recombinant canarypox expressing glycoproteins HA and F of the canine distemper virus (CDV) and 4 live attenuated viruses (Canine Adenovirus 2 -CAV2, Canine Parvovirus – CPV, Canine Parainfluenza Virus – CPiV, Canine Coronavirus - CCV) + liquid vaccine containing 2 inactivated Leptospira serovars (Icterohaemorrhagiae – Li; Canicola – Lc). Rabisin™: aluminum hydroxide adjuvanted inactivated vaccine against rabies.(Jean-Christophe ThibaultRABIES).

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Vaccines

Recombitek®C8: freeze-dried vaccine containing a recombinant canarypox expressing glycoproteins HA and F of the canine distemper virus (CDV) and 3 live attenuated viruses (Canine Adenovirus 2 -CAV2, Canine Parvovirus - CPV and Canine Parainfluenza Virus - CPiV) + liquid vaccine containing 4 inactivated Leptospira serovars (Icterohaemorrhagiae – Li; Canicola – Lc; Grippotyphosa – Lg; Pomona – Lp). Recombitek®C6/CV: freeze-dried vaccine containing a recombinant canarypox expressing glycoproteins HA and F of the canine distemper virus (CDV) and 4 live attenuated viruses (Canine Adenovirus 2 -CAV2, Canine Parvovirus – CPV, Canine Parainfluenza Virus – CPiV, Canine Coronavirus - CCV) + liquid vaccine containing 2 inactivated Leptospira serovars (Icterohaemorrhagiae – Li; Canicola – Lc). Rabisin™: aluminum hydroxide adjuvanted inactivated vaccine against rabies.(Jean-Christophe Thibault)ю

2. Vaccine The vaccine construct SPBN GASGAS is derived from SAD L16, a cDNA clone of the oral rabies virus vaccine strain SAD B19. SPBN GASGAS lacks the pseudogene (w). Also, all three nucleotides were changed at amino acid positions 194 and 333 of the glycoprotein; position 194 – AAT [Asn] ? TCC [Ser], position 333 – AGA [Arg] ? GAG [Glu] [14]. As a result of the genetic modification at position 333 of the glycoprotein the construct is apathogenic for immunocompetent mice after i.c. administration. The site-directed mutagenesis at position 194 prevents reversion to virulence. Furthermore, the construct contains a second identical glycoprotein gene with modifications as described above. It was predicted that the overexpression of the rabies virus glycoprotein increased not only its efficacy but also its safety profile by reducing potential risk of reversion to virulence and increase of apoptosis . Hence, the name SPBN GASGAS is derived from the introduced cloning sites (SmaI, PacI, BiswI and NheI), the two base exchanges (GA – glutamic acid, S – serine) and the expression of the two modified glycoprotein genes. Doses in the range of 106.0–109.1 FFU/ml SPBN GASGAS were used in the studies listed in Tables 1 and 2. The virus material was produced according to the protocol given by Vos et al . Material for overdose studies with titers >108.0 FFU/ml was concentrated via tangential flow filtration using ultrafiltration flat sheet cassettes with a Molecular Weight Cut Off (MWCO) of 300 kDa. The vaccine was administered by the oral route; some animals received the vaccine by direct oral instillation and other animals were offered a vaccine bait.

Prevention

Rabies is a fatal disease, so only timely therapeutic and preventive measures
("post-exposure prophylaxis") warn death in the victims. Category 1 contact involves exposure to biological animal fluids and secretions on intact skin. Since the transmission of the rabies virus in such cases is not occurs, this category of persons does not need to be preventive measures. Category 2 contact (minimal damage or
scratches on the skin without blood, squeezing open places on the skin) the vaccination course begins immediately and a local medical treatment of the injury site (exposition site). Externally healthy pets should be isolated; they are monitored for 10 days. If during this period the disease does not occur in animals, the course vaccination is stopped. Category 3 contact (transdermal bites or scratches with the appearance of blood, contact of mucous membranes or damaged skin with animal saliva, contact with volatile mice) the injury site is treated, immediate vaccination and administration of anti-rabies immunoglobulin. In persons with severe immune disorders (HIV-infected; patients on immunosuppressive therapy, etc.) contacts of the 2nd category are equated to contacts. High-quality and timely processing of the damage site significantly reduces the number of viable viruses and themes thereby reducing the risk of developing rabies. It includes prolonged (at least 15 minutes) washing of the wound with soap or other detergent, exposure to antiseptics (ethanol or iodine), effective primary surgical treatment of wounds. For human vaccination currently used only inactivated vaccines based on various fixed rabies virus strains (PV-11, RM, Vnukovo-32, etc.) strains are obtained on cell cultures, chicken or duck
embryos. For individuals at high risk of contact with rabid animals (employees of the veterinary service, workers involved in catching and maintenance of neglected animals, foresters, hunters, etc.) prophylactic administration of anti-rabies vaccine. Animals are immunized using live attenuated vaccines, inactivated vaccines, and genetic engineering vaccine.(Generalov.I.I)

CONCLUSION

In conclusion, it can be said that the percentage of patients suffering from rabies in medicine is very high. Methods such as RIF, ELISA and PCR, Rapid Fluorescent, Focus Inhibition Test (RFFIT), neutralization test, immunoelectrophoresis test are widely used in the diagnosis of rabies. Effective drugs for the treatment of rabies have not yet been developed, but a rapid vaccine and immune-enhancing drugs can be used to treat the

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virus. Therefore, it is considered the most correct way to introduce and follow preventive rules in order not to get the disease. Several pharmacological agents and vaccines have been developed as a result of many clinical studies and experiments conducted on patients suffering from this disease, but a number of works are being carried out to make them sufficiently effective. We hope that positive results will be achieved in the near future.

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