

Rabies a mini review

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ABSTRACT

Rabies is a zoonotic disease caused by infection with viruses of the genus *Lyssavirus*, transmitted through saliva of an infected animal, through bites and licking of mucous membranes or skin contact solutions. After its entry, viral multiplication occurs at the site of inoculation, subsequently invading the peripheral nervous system, and through centripetal migration it reaches the central nervous system where its replication occurs, causing encephalitis with neuronal degeneration of the spinal cord and brain that leads to death. In different parts of the world, dogs are an important reservoir of rabies virus, and dog bites are responsible for more than 99% of human cases. In Brazil, the main reservoir is vampire bats, and primary prevention involves the control of vampire bats combined with canine vaccination campaigns. In the event of human exposure to the rabies virus, post-exposure prophylaxis aims to prevent progression to clinical disease that involves wound care, administration of anti-rabies immunoglobulin and vaccination.

Keywords: Dogs; Bats; Rabies; Zoonosis; Vaccination

Abbreviations: WHO: World Health Organization; OPAS: Pan American Health Organization's; TNFRSF16: Tumor Necrosis Factor Receptor 16; NCAM: Neuronal Cell Adhesion Molecule; nAChR: Nicotinic Acetylcholine Receptor

Introduction

Rabies is a zoonotic disease caused by an RNA virus of the order *Mononegavirales*, family *Rhabdoviridae*, genus *Lyssavirus*, species *Rabies virus*. The rabies virus is typically transmitted by biting an infected land mammal to a susceptible host. Cases of rabies in humans are mainly caused by contact with dogs infected with the virus [1]. The main mode of transmission of the rabies virus occurs through exposure of injured skin to the saliva of an infected animal, usually a canine species [2], although in Brazil there are several case reports of transmission by vampire bats [3]. Rare cases of aerosol infection or organ transplantation have also been described in the literature [4]. In Brazil, the vast majority of viruses of *Lyssavirus* genus are found in different species of bats, such as *Desmodus rotundus*, *Diaemus youngi* and *Diphylla ecaudata*. In the 2000s, rabies in wild animals assumed greater importance, since between 2004-2005 *Desmodus rotundus* became the main transmitter of rabies in humans. Regarding bats, just the common vampire bats (*Desmodus rotundus*) are subject to control, being that other species are protected by law and only management

actions are recommended. In addition to bats, in the Northeast of Brazil the disease has been increasingly common in *Cerdocyon thous* (wild dog) and *Callithrix jacchus* (white-tufted marmosets) [5,6]. The rabies virus is believed to have evolved from a progenitor virus associated with bats, and host switching has led to the development of different variants of rabies virus [7,8]. Currently, seventeen main lineages are recognized in the world, with multiple variant forms [9].

Although vampire bat control and dog immunization campaigns have achieved a substantial reduction in the number of rabies cases in humans and animals, these viruses still continue to circulate, due to the lifestyle of vampire bats and the lack of interest on the part of entities government [10]. Scientific evidence indicates that the nicotinic acetylcholine receptor (nAChR), the neuronal cell adhesion molecule (NCAM), the metabotropic glutamate receptor subtype 2 (mGluR2) and a member of tumor necrosis factor receptor 16 (TNFRSF16) superfamily act as receptors to the entry rabies virus into different cell types [11-13]. After binding in the receptor, virus penetrates inside cells through a process of endocytosis, releasing its ribonucleocapsid

into cytoplasm where the negative RNA replicates, giving rise to messenger RNA (primary transcription cycle), which encodes five main proteins and new genomes, which are then encapsidated in cell membranes and released by budding [1]. The virus replicates at the site of inoculation initially in muscle cells and cells of subepithelial tissue, until it reaches sufficient concentration to reach the nerve endings, this extraneural replication time being responsible for the relatively long incubation period of rabies. In neuromuscular junctions through glycoprotein, the virus specifically binds in nicotinic acetylcholine receptor [14]. After this phase, the viruses reach the peripheral nerves, following a centripetal path towards the central nervous system. The virus follows retrograde axoplasmic flow through cell-to-cell transport [15].

The distribution of rabies virus in the brain is not homogeneous, therefore, the portion of tissue to be sent to the laboratory for diagnosis varies from species to species [16]. The most affected brain regions are the hippocampus, brain stem and cerebellum (Purkinje cells) [17]. In addition to the involvement of neurons in the central nervous system, the salivary glands are also affected, where the von Ebner glands and taste buds are considered sites of virus excretion in saliva of rabid dogs [18]. In the central nervous system, the virus spreads centrifugally to dorsal root ganglia, triggering sensations of pain, tingling and itching. When it spreads to peripheral nerves, it causes muscle weakness [1]. The rabies virus is able to survive, multiply and cause the death of neurons due to its ability to evade the adaptive immune system. Although neutralizing antibodies are present in cerebrospinal fluid, they are unable to control the infection. Rabies virus is a weak inducer of type I interferon synthesis, associated with increased expression of FasL and programmed cell death ligand 1 (PD-L1), which cause apoptosis of activated T cells [1,19,20].

Epidemiology

Rabies is a zoonosis that occurs endemically in several countries. Its epidemiological forms follow a didactic division, where the best known are urban rabies and rural rabies. Urban rabies is mainly transmitted from dog to dog. The virus is maintained primarily in the canine population, an important transmitter of virus to humans; however, other urban domestic animals can be infected [21]. In Brazil, rural rabies is maintained in the countryside mainly by the vampire bat *Desmodus rotundus*, which acts as a natural reservoir in rural environment. Other bat species such as *Cerdocyon thous*, *Callithrix jacchus*, *Tadarida brasiliensis*, *Myotis sp*, *Lasiurus sp*, *Artibeus sp* and primates such as *Callithrix jacchus* (white-tufted marmosets) also act as a wild reservoir of virus. Vampire bats in particular are capable of transmitting the virus to different species of domestic animals such as cattle, horses, goats and pigs [5,6,22]. Rabies virus transmission in bats is typically via saliva from one infected animal to another, and transplacental and transmammary transmissions in humans have been reported [23,24]. The different species of bats, hematophagous or not, are susceptible to the virus, with possibility of transmission and

presenting symptoms, which always leads to death [25]. The control of rabies cases in humans in Brazil was achieved through the control of vampire bats and dog immunization campaigns. However, due to governmental changes in this country, cases of human rabies have recently been described again.

In Brazil and other Latin American countries, from the 1980s onwards, anti-rabies vaccination campaigns were initiated in dogs and cats, which led to a sharp drop in the number of cases of infection and human death from rabies [26]. In 1999, 1200 dogs positive for the rabies virus were reported, and in 2012 this number fell to 11 cases [27]. In humans from 2010 to 2023, 47 cases of rabies were recorded in Brazil, and in 2014, there were no cases recorded. Of these 38 cases, the bat was described as the main transmitting animal [28]. In the year 2023, to date, two cases of human rabies have been reported in Brazil. The first case was in the municipality of Mantena/Minas Gerais, transmitted by a cattle infected with a bat variant (*Desmodus rotundus* genetic lineage), the second case was reported in Cariús/Ceará, a 34-year-old man attacked by a non-human primate (*Callithrix jacchus*). According to the Ministry of Health, the human mortality rate from rabies in 2022 was 0.00246/100 thousand inhabitants. Brazil records around 650,000 anti-rabies consultations per year [29]. In Latin America, the Pan American Health Organization's (OPAS) create the Regional Rabies Elimination Program in 1983, coordinated by Pan American Center for Foot and Mouth Disease and Veterinary Public Health (PANAFTOSA/SPV), and validated by Directors of Rabies Elimination Programs in Americas (REDIPRA) [26]. Through this action, the incidence of human rabies transmitted by dogs in Americas was reduced by 98%, from 300 cases reported in 1983 to three cases in 2023 [30]. Worldwide, it is estimated that 60,000 people die every year from this virus, with most cases located in Africa and Asia [1,31].

Clinical Manifestations

Two classic forms of rabies are recognized, the furious (encephalitic) form and paralytic form. After contact with the rabies virus, the incubation period may vary, depending on the location of virus entry and viral load, species, viral strain, and host immunological competence [1]. The initial symptoms occur due to viral replication in the dorsal root ganglia, leading to pain, paresthesia and/or itching. Next, the human being enters the acute neurological phase; in the furious form it presents intermittent agitation, hypersalivation and hydrophobia. In the paralytic form, there is muscle weakness and paralysis. The natural evolution of these two clinical forms of rabies are coma and death [1,2]. The incubation period in humans, in most cases, is 2 to 12 weeks, and can vary from 10 days to 4 to 6 years. During the incubation period, the patient is asymptomatic. The longer or shorter duration of period depends on the dose of virus inoculated by bite, location, and severity of injury, with the period being longer the further away the injury from the central nervous system occurs [32]. The incubation period in dogs varies from 15 days to 2 months. In prodromal phase, the animals show changes in behavior; hide in dark plac-

es, or show unusual agitation. Dogs present anorexia, irritation and itching in the region where the virus penetrates and a slight increase in temperature. After one to three days, the dog becomes aggressive, with a tendency to bite objects, animals, humans, and itself, causing serious injuries. Salivation becomes abundant due to paralysis of swallowing muscles.

There is a change in barking, which becomes hoarse or bitonal, due to partial paralysis of vocal cords. Dogs infected with rabies virus are prone to abandoning their homes and traveling long distances, where they can attack other animals. In the final phase of disease, generalized convulsions occur followed by motor incoordination and paralysis of trunk and limbs. The mute form is characterized by predominance of paralytic-like symptoms. The paralysis begins in head and neck muscles; the animal presents difficulty swallowing, followed by paralysis and death [33]. In cattle, rabies is transmitted by vampire bats, and the incubation period is generally longer, ranging from 30 to 90 days or even longer. The predominant symptomatology is the paralytic form. Infected animals move away from the herd, have dilated pupils, tearing, nasal phlegm, bristly hair and abnormal movements of hind limbs. They may also present restlessness, muscle tremors and hypersensitivity at the site of the bite, where animals can cause self-laceration. As disease progresses, tonic-clonic contractions, motor incoordination, difficulty swallowing, and interruption of rumination appear. Signs of paralysis appear between the second and third day after onset of symptoms, lasting two to five days [34]. The symptoms of rabies in horses, sheep and goats are like those in cattle. In pigs, the disease generally begins with symptoms of excitability. The animals appear aggressive, like what happens in dogs [35].

In bats, a phase of excitability can occur followed by paralysis, especially of the wings, which causes these animals to stop flying. Bats (hematophagous or not) found in unusual places and times and that are not capable of avoiding obstacles placed in their path should be suspected [33].

Diagnosis

Although clinical symptoms of hydrophobia or aerophobia are indicative of rabies virus infection, only laboratory findings can provide a definitive diagnosis [1]. From replication in the central nervous system, the rabies virus continues in a centrifugal direction, spreading through the peripheral and autonomic nervous system to different organs (lungs, heart, kidneys, bladder, uterus, testicles, hair follicle) and salivary glands, being eliminated through saliva. Dissemination allows the virus to affect sensory nerve endings in the skin tissue of the head and neck, where the presence of viral antigen can be demonstrated [36]. Therefore, tissue biopsy from this region is used as an ante-mortem diagnostic method. The virus can also be present in retina and corneal epithelium [37]. For ante-mortem diagnosis, tissue samples obtained from neck skin biopsies and saliva can be used [36]. In dogs infected with rabies virus, high viral titers can be detected in

saliva up to 10 days before the onset of clinical illness [38]. Skin and saliva samples can be tested for the presence of viral antigen (nucleoprotein), or viral RNA by RT-PCR and RT-qPCR in neurons near hair follicles. Currently, the use of corneal impression is not recommended. Likewise, detection of specific antibodies against virus in cerebrospinal fluid has a limited value [1]. To the post-mortem diagnosis, it is essential to obtain brain tissue and histopathology with Sellers staining to investigate the presence of Negri corpuscle [39].

Its absence, however, does not invalidate the diagnosis of rabies, considering that in episodes of rapid evolution, with a short incubation period and early death, there may not be enough time for the inclusions to appear. This fact has been frequently observed in the post-mortem diagnosis of rabies in horses [40]. Areas of vacuolization can also be observed, giving the central nervous system a spongiform appearance [41]. In ruminants with suspected rabies, the entire brain, or fragments of the central nervous system such as the cortex, cerebellum and hippocampus or Ammon's horn must be collected from both hemispheres [42]. In horses, the medulla oblongata, and fragments of initial, medial and terminal portions of spinal cord must also be sent [43]. In dogs, the preferred portion is the Ammon's horn or the hippocampus [44]. It should be noted that, when collecting samples from all species (domestic or wild), a portion of the marrow must be sent. The World Health Organization (WHO) and the World Organization for Animal Health (OIE) recommend the fluorescent antibody test to search viral antigens in impressions from fresh samples of brain tissue (Ammon's horn), but this test requires high-cost equipment, unavailable in laboratories with limited resources, which led to the production of direct immunohistochemical test (dRIT) that uses a common optical microscope [45]. Other tests include RT-PCR [38,46], test for isolation of rabies virus in cell culture using mouse neuroblastoma cells (N2A) and the test for isolating rabies virus in mice (biological test) [47].

In the case of human rabies transmitted by vampire bats, whose form is predominantly paralytic, the diagnosis is uncertain, and the suspicion lies in other diseases that can be confused with human rabies. In these cases, differential diagnosis for tetanus must be carried out; Guillain-Barré syndrome; pasteurellosis due to cat and dog bites; infection with virus B (*Herpesvirus simiae*) from monkey bites; botulism; and rat bite fever (*Sodóku*) [39,48].

Prevention

In Brazil, the main form of prevention against the rabies virus includes controlling vampire bats and carrying out canine vaccination campaigns [1]. For travelers and professionals at risk of exposure to the rabies virus, pre-exposure prophylaxis through immunization is recommended [49]. The vaccine is indicated for individuals at risk of permanent exposure to rabies virus; occupational activities such as professionals and assistants in virology and anatomopathology laboratories for rabies; professionals who work in catching chiropterans;

veterinarians and other professionals who work constantly at risk of exposure to the rabies virus (zootechnicians, agronomists, biologists, zoo/environmental park employees, cavers); veterinary medicine students and students who work in the capture and management of wild mammals that potentially transmit rabies; professionals working in epidemic area for canine rabies variants 1 and 2, with records of cases in the last 5 years in the capture, containment, handling, sample collection, vaccination of dogs, which may be victims of attacks by dogs. Tourists traveling to endemic or epidemic areas for the risk of rabies transmission, especially canine, must be individually assessed and may receive pre-exposure prophylaxis, depending on the risk to which they will be exposed during the trip [1,49-51]. In Brazil, there are different inactivated rabies virus vaccines for the immunization of humans and domestic animals [52]. In Europe and the United States, subunit vaccines are available for vaccinating wildlife animals [53,54].

For humans who have been exposed to the virus, there are freeze-dried inactivated vaccines, based on cell culture that have greater antigenicity, reducing the number of doses necessary to obtain a protective response and reduction in the number of clinical visits, which increases patient adherence [55,56]. Due to the high fatality rate (close to 100%) and high incidence of cases of rabies virus infection in children <15 years of age, some studies suggest pediatric vaccination is recommended in high-risk endemic regions. Some studies also consider rabies to be a neglected pediatric disease, since half of the deaths occur in children under 15 years of age, who, when interacting with domestic or street dogs, are more susceptible to being bitten [57,58].

Treatment

In the event of an accident caused by a bite by an animal suspected of having rabies, it is recommended to vigorously clean the wound with soap and water, remove foreign bodies, and use antiseptics based on polyvinylpyrrolidone iodine, povidine and chlorhexidine digluconate or iodinated alcohol. These substances should only be used during the first consultation. In the following cases, general care should be carried out guided by the health professional, according to the assessment of the injury [1,59]. The rabies virus is sensitive to lipid solvents (soap, ether, chloroform and acetone), 45-70% ethanol, iodinated preparations and quaternary ammonium compounds. The rabies virus is very sensitive to physical and chemical agents, and it can be inactivated in a few minutes by the action of strong acids and bases, sunlight, changes in pH, temperature and ultraviolet rays [60]. If exposure is suspected, medical attention should be sought to assess the need for post-exposure prophylaxis. This prophylaxis includes administration of anti-rabies immunoglobulins at the wound site and vaccination. Greater care is needed in patients on hemodialysis and immunocompromised to obtain an adequate immune response [61-63]. If domestic animals are suspected of being exposed to the rabies virus, the animal must be observed for the appearance of clinical signs characteristic of the disease for 10 days and post-exposure pro-

phylaxis must be initiated in humans. If the animal remains healthy after the quarantine period, treatment can be stopped second medical criteria [64]. In humans, when the clinical signs and symptoms of rabies become evident, the patients' prognosis is usually unfavorable, culminating in death within a period between 5 and 11 days [65].

Considerations

In Brazil, there is a lack of assistance to vulnerable populations and surveillance of rabies in its wild cycle, although significant advances have been made in relation to the diagnosis and treatment of human beings who have had contact with the rabies virus. Its prevention involves educating the population about etiological agents, transmission form, control of vampire bats and immunization of canine population.

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