

Rabies a Zoonotic disease, Transmission, Prevention, and Treatment

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Abstract: Rabies a zoonotic disease prevalent worldwide, with high mortality, more than a third of global toll in India. Dogs are the common animals involved. In Americas, bat bites are the most common source of rabies infection in humans. Rabies is caused by lyssaviruses including rabies virus and Australian bat lyssavirus. Disease produces almost fatal encephalitis in humans and in other mammals. From the point of entry, the virus is neurotropic, travelling along neural pathways into the central nervous system. After the brain infected virus travels centrifugally to the peripheral and autonomic nervous system, and migrating to salivary glands, ready to be transmitted to the next host. Incubation period as short as four days and longer than six years Symptoms soon expand to slight or partial paralysis, anxiety confusion, hallucination and delirium. Survival is rare once symptoms have presented even with the intensive care. Hydrophobia is associated with furious rabies (80%), and 20 % experience paralytic rabies marked by muscle weakness .RT PCR assays are sensitive and specific for routine diagnostic test. Control includes vaccinating the dogs, cats and control of the strays. Post-exposure prophylaxis (PEP) given without delay is 100 % effective against rabies. CDC recommends people receive one dose of human rabies immunoglobulin (HRIG) and four doses of rabies vaccine over a 14-day period.

Keywords: Rabies, Transmission, Prevention, Vaccination,

I. Introduction

Rabies, Latin for “madness” derives from rabere, torare, and is related to Sanskrit word for violence, rabhas. The Greek term for rabies, lyssa, also means madness. And it provides the genus name (Lyssavirus) [1,2]. Rabies a viral disease that produces an almost uniformly fatal encephalitis in humans and almost other mammals. It has been present throughout recorded history, and literature, and likely predates the evolution of humans [1]. The rabies is caused by lyssaviruses including rabies virus and Australian bat lyssavirus [3]. Rabies is spread when an infected animal scratches or bites another animal or human [4]. Saliva from an infected animal can also transmit rabies if saliva comes into contact with mouth, nose, or eyes [4]. Globally dogs are the most common animal involved. More than 99% of rabies cases in countries where dogs commonly have the disease are caused by the dog bites [4,5]. Rabies causes about 26,000 to 55,000 deaths [4,]. More than 95% of these deaths occur in Asia and Africa [4]. Rabies is present in more than 150 countries and on all continents but Antarctica [4]. In the Americas, bat bites are the most common source of rabies infections in humans, and less than 5% of cases from dogs [4]. Rodents are very rarely infected with rabies [5]. The rabies virus travel to the brain by following the peripheral nerves. The disease can only be diagnosed after the start of the symptoms [4]. Rabies cause acute inflammation of the brain in humans and other warm-blooded animals, followed by violent movements, uncontrolled excitement, fear of water, an inability to move parts of the body, confusion, and loss of consciousness [4]. Treatment with one dose of human rabies immunoglobulin (HRIG) and four doses of rabies vaccine over a 14-day period [6]. Prevention include vaccinating, dogs cats, and ferrets against rabies, and avoid handling wild animals or strays [7]. Paper reviews the transmission, prevention and treatment of rabies and a reference to recent rabies outbreak in Malaysia..

II. History and epidemiology

The Babylon Eshnuna code contains the first known mention of rabies in the 23rd century BC. Democritus provided a clear description of animal rabies in 500 BC. Wound cauterization was the preferred treatment in the 1st century AD and was recommended for the management of rabid animal bites until the 20th century [2]. The first written record of rabies in the Mesopotamian Codex of Eshnuna (circa 1930 BC), which indicates that the owner of a dog showing symptoms of rabies should take preventive measure against bites. If other person were bitten by a rabid dog and later died, the owner was heavily fined [8].

Rabies in the Western Hemisphere predated Columbus but remained rare because of low population density [9]. It appeared to have originated in the old World, the first epizootic in the New World occurring in Boston in 1768. It spread from there, over the next few years to various other states, as well as to the French West Indies, eventually becoming common all across North America [10].

Bats spread the disease among cattle and humans in Central America in the early 16th century [11]. Rabies epizootic began in the northern and the eastern United States in the 19th century, reflecting the importation of foxes for hunting [12]. Globally, 99% of all cases of human rabies result from transmission from dogs [1]. In Central and South America, the vampire bat is a principal vector of rabies for both humans and domesticated animals and is estimated to cause losses in cattle exceeding 40 million annually. In Canada, where canine rabies was the primary problem from 1920 to 1950, a shift to wildlife rabies, primarily in skunk and foxes, was reported following widespread disease in foxes in Arctic areas [13].

Rabies was considered a scourge for its prevalence in the 19th century. In France and Belgium, where Saint Hubert was venerated, the "Hubert key" was heated and applied to cauterized wound. By an application of magical thinking dogs were branded with the key in hopes of protecting them from rabies. The fear of rabies was irrational, due the insufficient vectors (mostly rabid dogs) and the absence of any efficacious treatment. It was not uncommon for a person bitten by a dog but merely suspected of being rabid, to commit suicide or to be killed by others [14]. This gave Louis Pasteur ample opportunity to test post exposure treatment from 1885 [15].

An estimated 20,000 people die every year from rabies in India more than a third of global toll [16]. As of 2007, Vietnam had second-highest rate, followed by Thailand; in these countries, the virus is primarily transmitted through canines (feral dogs and other wild canines species) [17]. Another source of rabies in Asia is the pet boom. In 2006 China introduced population control for dogs in Beijing [18]. Rabies virus survives in widespread, varied natural fauna reservoirs. It is present in the animal populations of almost every country in the world except in Australia and New Zealand. Australian bat lyssavirus (ABLV), discovered in 1996, is similar to rabies and is believed to be prevalent in native bat populations [19]. In the United States, one to four cases were reported annually in the past decade, and the sources of human cases have changed from predominantly domestic animals (1945 to 1965) to largely unknown sources (1976 to present). Three cases of human rabies were reported from Texas, Indiana, and California during 2006. The cases from Indiana and Texas were from bat rabies variants. The case in California was canine rabies acquired in the Philippines [20]. In 2003, a 21 year-old man in Virginia died of raccoon strain of rabies, no history of animal exposure could be elicited from patient's family or acquaintance [21]. In Malaysia (September, 2015), three districts, Penang, Perlis and Kedah has been declared a rabies infected, with two rabies cases reported in Penang, and 443 dogs vaccinated [22].

III. Viral etiology

Three genera infect animals (lyssavirus, vesiculovirus, and Ephemerovirus). Rabies (serotype 1) is the type species of the lyssavirus genus [12]. Australian bat lyssavirus (ABLV) is generally distinct from rabies virus but causes rabies-like disease in Australian flying foxes and insectivorous bats. Two human deaths in Australia both after a rabies like illness, were ABLV infection acquired from animals [23]. Lyssaviruses have helical symmetry with a length of about 180 nm and a cross section of 75 nm [24]. These viruses are enveloped and have a single stranded RNA genome with negative sense. The genetic information is packed as a ribonucleoprotein complex in which RNA is tightly bound by the viral nucleoprotein. The RNA genome of the virus encodes five genes whose order is highly conserved nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and the viral RNA polymerase (L) [25]. Once within a muscle or nerve cell, the virus undergoes replication. The trimetric spikes on the exterior of the membrane of the virus interact with a specific cell receptor, the most likely one being the acetylcholine receptor, acetyl. The cellular membrane pinches in a process known as pinocytosis and allows entry of the virus into cell by way of an endosome. The virus then uses the acidic environment, which is necessary, of that endosome and binds to its membrane simultaneously, releasing its five proteins and single strand RNA into the cytoplasm [26].

The L protein then transcribe five mRNA strands and a positive strand of RNA all from the original negative strand RNA using free nucleotides in the cytoplasm. These five strands are then translated into their corresponding proteins (P, L, N, G, and M proteins) at free ribosomes in the cytoplasm. Some proteins require post-translative modifications. For example, the G protein travels through the rough endoplasmic reticulum, where it undergoes further folding, and is then transported to the Golgi apparatus, where a sugar group is added to it (glycosylation) [26]. Where there are enough proteins, the viral polymerase will begin to synthesize new negative strands of RNA from the template of the positive strand RNA. These negative strands will then form complexes with N, P, L and M proteins and then travel to the inner membrane of the cell, where a G protein has embedded itself in the membrane. The G protein then coils around the N-P-LM complex of proteins taking some of the host cell membrane with it, which will form the new outer envelope of the virus particle. The virus then buds from the cell [26].

From the point of entry, the virus is neurotropic, traveling quickly along neural pathways into the central nervous system. The virus usually first infects muscle cells close to the site of infection, where they are able to replicate without being “noticed” by the host’s immune system. Once enough viruses has been replicated, they begin to bind to acetyl choline receptors (p75NR) at the neuromuscular junction [27].The virus then travels through the nerve cell axon via retrograde transport, as its P protein interacts with dynein, a protein present in the cytoplasm of nerve cells. Once the virus reaches the cell body it travels rapidly to the Central Nervous System (CNS), replicating in motor neurons and eventually reaching to the brain. After the brain is infected, the virus travels centrifugally to the peripheral and autonomic nervous systems, eventually migrating to the salivary glands, where it is ready to be transmitted to the next host [28].

IV. Transmission

All warm- blooded species, including humans, may become infected with rabies virus and develop symptoms. Birds were first artificially infected with rabies in 1884, however birds are largely if not wholly asymptomatic, and recover [29].Other bird species have been known to develop rabies antibodies, a sign of infection, after feeding on rabies-infected animals [30].Virus can also grow in cells of poikilothermic(cold blooded) vertebrates[31].Most animals can be infected by the virus and can transmit the disease to humans. Infected bats, monkeys ,raccoons, foxes, skunks, cattle, wolves, coyotes, dogs, mongoose(normally yellow mongoose) and cats present the greatest risk to humans [32,33].Rabies may spread through exposure to infected domestic farm animals, groundhogs, weasels ,bears, and other wild carnivorans.Small rodents, such as squirrels, hamsters, guinea pigs, gerbils, chipmunks,rats,and mice ,and lagomorphs such as rabbits and hares,are almost never found to be infected with rabies and not known to transmit rabies to humans, bites from these rodents rarely require rabies prevention[34,35].

The virus usually present in the nerves and saliva of a symptomatic rabid animal. The route of infection is usually, but always by a bite. In many cases, the infected animal is exceptionally aggressive, may attack without provocation, and exhibit otherwise uncharacteristic behavior [36,37].Transmission between humans is extremely rare. A few cases have been recorded through transplant surgery [38].After a typical human infection by bite; the virus enters the peripheral nervous system. It then travels along the afferent nerves toward the central nervous system [39].

V. Pathophysiology

Rabies infection begins with centripetal spread of virus via peripheral nerves to the CNS, proliferation within the CNS, and centrifugal spread via peripheral nerves to many tissues. After the virus enters through the break in the skin, across a mucosal surface, or through the respiratory tract, it replicates in muscle cells and so doing, infects the muscle spindle. It then infects the nerve that innervates the spindle and moves centrally within axon of these neurons. Replication occurs in peripheral neurons, but not usually in Gila, either peripheral or central. Virus present in dorsal root ganglia within 60 to 72 hours of inoculation and before its arrival in spinal cord neurons, which confirms its transport within sensory neuron [40,41].Some studies confirm that neuromuscular junction is also a major site of neuronal invasion and blocking acetylcholine receptors inhibits viral attachment [42,43].Partial sequence homology exists between rabies virus glycoprotein and several snake neurotoxins that bind to the receptor. However, rabies virus can enter neurons that do not express acetylcholine receptors, albeit with less efficiency, which indicates the existence of other receptors [44,45].

After CNS infection, virus spreads to the rest of the body via peripheral nerves. The high concentration of virus in the saliva results from viral shedding from sensory nerve ending in the oral mucosa and also replication in the salivary glands [46].The mechanism by which rabies damage the CNS are obscure because pathologic evidence of neuronal necrosis is frequently minimal or absent [47].Rabies may interfere with neurotransmission and endogenous opioid systems [48,49],and almost 30 fold increase in the nitric oxide production suggest an excitotoxicity mechanism. An inverse relationship is found between the concentration of G protein produced and pathogenicity of different viral strains, and a monotonic relationship is found between pathogenicity and the induction of neuronal apoptosis [50,51].the infection is also capable of inducing apoptosis in T lymphocytes, which may relate to the failure of the immune response to control the disease[52].

In furious rabies brain usually appears unremarkable grossly except for the vascular congestion [53].The microscopic pathology of rabies is typically encephalitis with Negri bodies. However, not all autopsy specimens show the perivascular lymphocytic cuffing and necrosis that characterize encephalitis and some cases look histologically like meningitis[54].Negri bodies are concentrated in hippocampal pyramidal cells and less frequently in cortical neurons and cerebellar Purkinje cells[53].They are round or oval, usually eosinophilic,cytoplasmic inclusions between 1 and 7µm across, and they contain viral nucleocapsids[55].The acidophilic lyssa body is ultrastructural identical to the Negri body[56].Negri bodies and lyssa bodies are detected in only a relatively small percentage of the cells that are infected determined by immunohistochemistry[57].

Paralytic rabies affects primarily the spinal cord, with severe inflammation and necrosis [58]. The brain stem is involved to a lesser extent. A few patients have cortical Negri bodies. Segmental demyelination occurs in the peripheral nerves and resembles acute inflammatory polyneuropathy (Guillain-Barre syndrome). Systemic pathology is most remarkable for the presence of myocarditis [59]. The cardiac disorder resembles the myocarditis that occurs in hypercatecholaminergic states such as pheochromocytoma, subarachnoid hemorrhage and tetanus [60]. Negri bodies are found in the hearts of some patients, which suggest that a direct viral role in this condition [61]. Atrial ganglioneuritis suggest that virus reaches the myocardium via spread from the nervous system [62].

VI. Clinical manifestations

Several variables affect the risk of rabies and the rate of clinical disease development after exposure to a rabid animal [63]. The viral inoculum is important, reflected by the relationship between the extent of exposure to the saliva and the rapidity of progression. The location of bite also influences the risk of rabies: bites on the face are more likely to result in disease than those on the extremities [64]. The period between infection and the first flu-like symptoms is typically 2 to 12 weeks. Incubation periods as short as four days and longer than six years have been documented, depending on the location and severity of the contaminated wound and the amount of virus introduced. Signs and symptoms may soon expand to slight or partial paralysis, anxiety, insomnia, confusion, agitation, abnormal behavior, paranoia, terror, and hallucinations, progressing to delirium [29]. Death mostly occurs 2 to 10 days after first symptoms. Survival is rare once symptoms have presented, even with the administration of proper and intensive care [65]. Jeanna Giese, who in 2004 was the first patient treated with the Milwaukee protocol became the first person ever recorded to have survived without receiving successful post-exposure prophylaxis. An intention to-treat analysis has since found this protocol has a survival rate of about 8% [66,67]. Prolonged survival of up to 133 days has been reported after the use of intensive respiratory care to prevent hypoxia [68].

Hydrophobia (fear of water) is the historic name for rabies. Any mammal infected with the virus may demonstrate hydrophobia [69,70]. Hydrophobia is commonly associated with furious rabies that affect 80% of the infected people. The remaining 20% may experience a paralytic form of rabies that is marked by muscle weakness, loss of sensation, and paralysis. This form of rabies does not usually cause fear of water (hydrophobia) [70]. Once the patient become symptomatic treatment is almost never effective and mortality is over 99%. Rabies may also inflame the spinal cord, producing transverse myelitis [71].

VII. Diagnosis

Diagnosis of rabies can be difficult, because in the early stages, it is easily confused with other diseases or with aggressiveness [72]. Frequently used method recommended by World Health Organization (WHO) fluorescent antibody test –FAT or FRT (fluorescent rabies test) The FAT relies on the ability of a detector molecule (usually fluorescein isothiocyanate). Microscopic analysis of samples is the only direct method that allows for identification of rabies virus-specific antigen in a short time and at a reduced cost. Autolyzed samples can, however, reduce the sensitivity and specificity of FAT [73]. The RT-PCR assays proved to be a sensitive and specific tool for routine diagnostic purpose [74]. Differential diagnosis in a case of suspected human rabies may initially include any cause of encephalitis, in particular infection with viruses such as herpesviruses, enteroviruses, and arboviruses and other [75].

VIII. Prevention and Control

Rabies vaccine was developed in 1885 by Louis Pasteur and Emile Roux, prior to that most human cases of rabies were fatal. The original vaccine was harvested from infected rabbits from which the virus in the nerve tissue was weakened by allowing it to dry for five to ten days [76]. Human diploid cell rabies vaccine was started in 1967. Less expensive chicken embryo cell vaccine and purified Vero cell rabies vaccine are now available [77]. A recombinant vaccine called V-RG has been used in Belgium, France, Germany, and the United States to prevent outbreaks in undomesticated animals [78]. Immunization before exposure has been used in both human and nonhuman populations where, as in many jurisdictions, domesticated animals are required to be vaccinated [79]. Following measures in the annual report of Missouri Department of Health and Senior Services Communicable Disease Surveillance 2007 [7], can help reduce the risk of contracting rabies:

(a) vaccinating dogs, cats, and ferrets against rabies (b) keeping pets under supervision (c) not handling wild animals or stray (d) contacting animal control officer (or veterinary department) upon observing a wild animal or stray, especially if the animal is acting strangely (e) if bitten by an animal, washing the wound with soap and water for 10 to 15 minutes, and seek help from a healthcare provider.

IX. Treatment and Prognosis

Treatment after exposure can prevent the disease if administered promptly within 10 days of infection[24]. Thoroughly washing wound with soap and water as soon as possible, is effective in reducing the viral particles, povidone-iodine or alcohol is recommended to reduce the virus further[80,81]. In the US, the Centers for Disease Control and prevention recommends people receive one dose of human rabies immunoglobulin (HRIG) and four doses of rabies vaccine over a 14-day period[26]. HRIG should be injected around the bites, with reminder being given by deep intramuscular injection at a site distant from the vaccination site[26,rpt]. Intramuscular vaccination should be given into the deltoid, not gluteal area, which has been associated with vaccination failure due to injection into fat rather than muscle. In infants, the lateral thigh is recommended [82]. Post-exposure prophylaxis (PEP) given without delay is 100% effective against rabies[66]. High mortality has been reported in India due to late arrival in the hospital because of intervention of faith healers[83].

Prognosis. In unvaccinated humans, rabies is almost always fatal after neurological symptoms have developed[84]. Vaccination after exposure, PEP, is highly successful in preventing the disease if administered promptly in general within 6 days of infection[66]. In the case of significant delay in administering PEP, the treatment still has a chance of success[26].

X. Conclusion

Rabies a vector borne disease with high mortality in unvaccinated humans treatment with one dose of human rabies immunoglobulin (HRIG) and four doses of vaccination over 14-day period. Vaccination of dogs, cats, domestic pets and control of strays helps in the successful rabies control.

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