Title: # Rabies in canines with special reference to wild animals

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Abstract

Rabies is one of the oldest zoonotic disease which continues to pose a significant threat to animals and humans in most parts of the world affecting the central nervous system. Rabies otherwise 'rabere' in Latin means 'to be mad.' The disease is known since the advent of civilization. The first official documentation of rabies appeared in the pre-mosaic Eshmuna code of Babylon in the twenty-third century BC. However, it was Louis Pasteur in 1880's who identified a virus as the cause of the disease. Though rabies is a preventable viral zoonosis by vaccines still it remains an important public health issue in the developing countries which is evident from the fact that globally this devasting disease is responsible for more than 60,000 human deaths, while approximately 15 million people receive rabies post exposure prophylaxis (PEP) annually (Dietzschold et al. 2003; Kuzmin et al. 2005; Wilde et al. 2013). Despite of global vast attempt and implementation of extensive control schemes and public health awareness programmes, still over 95% of the mortality happens in Asia and Africa, where canine rabies is enzootic (WHO 2016). In India, about 20,000 human deaths occur each year by the bite of rabid dog (Sudarshan et al. 2006). Rabies in human always occurs as fatal disease inspite of advanced therapeutic measures. Based on severity of mortality in humans, rabies stays in seventh position among the infectious diseases present in the globe (Wyatt 2007).

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SPECIAL ARTICLE

Rabies in canines with special reference to wild animals

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Introduction

Rabies is one of the oldest zoonotic disease which continues to pose a significant threat to animals and humans in most parts of the world affecting the central nervous system. Rabies otherwise 'rabere' in Latin means 'to be mad.' The disease is known since the advent of civilization. The first official documentation of rabies appeared in the pre-mosaic Eshmuna code of Babylon in the twenty-third century BC. However, it was Louis Pasteur in 1880's who identified a virus as the cause of the disease. Though rabies is a preventable viral zoonosis by vaccines still it remains an important public health issue in the developing countries which is evident from the fact that globally this devasting disease is responsible for more than 60,000 human deaths, while approximately 15 million people receive rabies post exposure prophylaxis (PEP) annually (Dietzschold et al. 2003; Kuzmin et al. 2005; Wilde et al. 2013). Despite of global vast attempt and implementation of extensive control schemes and public health awareness programmes, still over 95% of the mortality happens in Asia and Africa, where canine rabies is enzootic (WHO 2016). In India, about 20,000 human deaths occur each year by the bite of rabid dog (Sudarshan et al. 2006). Rabies in human always occurs as fatal disease inspite of advanced therapeutic measures. Based on severity of mortality in humans, rabies stays in seventh position among the infectious diseases present in the globe (Wyatt 2007).

Globally, information are increasing on the roles of wild animals in the epidemiology of rabies particularly in the developing world, for instance, rabies transmission risks and its link with wild animals have been enumerated by Caron et al. (2013). Hanlon (2006) in their epidemiological survey observed the limitations associated with rabies control given the compounded factors associated with wildlife and its ecology. They recommended a multiagency approach in the management and understanding the epidemiology of rabies and wildlife. The team also pointed out some constrains on available and feasible control methods compared with the broad range of public attitude and engagement in wildlife ventures and recreational activities and suggested that the control of wildlife rabies should be multiagency and multidisciplinary (Hanlon et al., 2006). Other scientists emphasized the fact that rabies have a multi-hosts and multiinfections scope with significant impacts on human efforts are difficult for the management and control of rabies in domesticated particularly in the wildlife (Martin et al., 2011).

Sylvatic zoonosis incude all those diseases having reservoirs among both in wild or feral animals. Free living and captive Status of sylvatic rabies in India is alarming and the disease has been recorded in zoo animals (Pandit, 1950). Study of epidemiology of sylvatic rabies in India revealed that deer, camel, bear, elephant, fox, hyena, jackal, lion, monkeys, panther, leopard, tiger, zebra etc were the animals suspected to transmit the rabies to human. Wolves and hyenas were considered as most dangerous wild animals as per as human fatalities are concern (Joshi, 1991)

Etiology and Epidemiology

Rabies in mammals is fatal due to involvement of nervous system (NS) and is caused by a neurotropic, negative sense, non-segmented, single-stranded RNA virus that belongs to the Lyssa virus genus of the Rhabdoviridae family and Mononegavirale order (Madhusudana et al. 2012). The interesting feature of the lyssa virus is presence of seven distinct genotypes. The rabies virus (RABV) genome is approx. 12 kb size, which carries five structural proteins namely, nucleo protein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and RNA-dependent RNA polymerase (L) (Albertini et al. 2011). The RABV genome composed of N, P and L proteins, which forms ribonucleoprotein complex that helps in multiplication of virus in the cytoplasm of host cells. The G protein of the RABV is alone expressed on the viral surface, which is

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responsible for the viral pathogenicity, and induces protective immunity against rabies (Albertini et al. 2011; Zhu and Guo 2016). However, still the chance of increase in the number of these viruses is possible with more widespread and intensive sampling. It specifically causes acute encephalomyelitis affecting primarily carnivores and bats but has got the capability to affect all warm-blooded animals including humans as well as a wide variety of wildlife species that act as reservoirs for infection predominantly and it influences the population dynamics accordingly (Rupprecht and Gibbons 2004). Significance of rabies lies in the facts that it is mostly fatal with no specific antiviral treatment and is distributed globally (Greene, 2006). In Asia and Africa, the disease raises a burning public health issues. In the Asian subcontinent, it is predominantly high in Bangladesh and India followed by Nepal, Myanmar, Bhutan, Thailand and Indonesia, wherein it is prevalent moderately. Its prevalence has been documented from 20% to 50% in different species of domestic animals. Wild animals accounted for 92.7% of reported cases of rabies in 2018. Bats were the most frequently reported rabid wildlife species (33% of all animal cases during 2018), followed by raccoons (30.3%), skunks (20.3%), and foxes (7.2%). RABV is maintained in most parts of the world by mesocarnivores (animals whose diet consists of 50–70% meat), including dogs, foxes, raccoon dogs, raccoons, mongooses and skunks (CDC, 2020).

The susceptibility of animals varies greatly depending upon the animal species, genetic makeup, animal's age, strain, biotype or dose of the virus and exposure route. Worldwide rabies is endemic, which is a major concern but in countries like USA control programmes have facilitated the process of reducing the number of cases (Sudarshan et al. 2006; WHO 2016). In many developing countries, mortality in humans due to rabies infection are low because of under-reporting, cultural beliefs, poor or inadequate rabies diagnostic units and poor knowledge on the mode of transmission and prevention of the disease. Under-reporting of rabies in endemic developing countries has resulted in the disease being ignored by medical professionals and subsequently poor assistance from international community and donor agencies (Ototorin et al. 2015).

Reservoirs of Rabies virus

Bats:

Rabies virus transmitted to human are increasingly being done by bats, over 140 variants have been identified in insectivorous bats. Transmission of rabies virus can occur from bat bites that may be small and insignificant (CDC, 2008). Due to this man and other animals' contact with bats should be limited; they should only be handled by trained and vaccinated persons and should not be kept as pets (CDC, 2008). Terrestrial animals inflict more visible wounds from bites compared to bats which make the assessment of the risk of contracting rabies from bat encounter to be difficult (Artois et al., 2011). Any animal bitten or scratched by bat should be regarded as exposed (CDC, 2010).

Wild terrestrial carnivores:

Wildlife species of special concern in Nigeria include Jackals and mongooses (Dzikwi et al., 2010). Wildlife such as several species of bats, coyotes, foxes racoons and skunks account for the occurrence of most of the rabies cases in USA. The clinical signs exhibited by wildlife are not well documented therefore scratches and bites from wildlife and their crosses should be taken as possible rabies exposure (CDC, 2008).

Other wild animals:

Squirrels, chipmunks, rats, mice, hamsters, guinea pigs, gerbils, rabbits and hares are not usually infected with rabies (Wu et al., 2009). Crosses of wildlife and other domestic animals are regarded as wild animals (NASPHV, 2007). Due to the fact that the duration of time of shedding of rabies virus in wild animal crosses is unknown their bite in human should be followed by rabies testing of the hybrid animal, euthanasia or vaccination which should be discontinued if the animals involved are not positive for rabies (CDC, 2008).

Transmission

The disease is nearly always caused by the bite of an infected animal that has rabies virus in its saliva. Other modes of transmission are infrequently involved in infections of the dog and cat but may serveto maintain infection in wild animal. Transmission from exhaled or excreted virus has been suggested for spread between animals in extremely large colonies of cave-dwelling bats and by infections after laboratory exposures. Such air borne infections probably involve large quantities of aerosolized virus under conditions of poor ventilation and a susceptible exposed host. Rabies can occasionally result from ingesting infected tissue or secretions. Suspected transplacental rabies infections in skunks and bats, have been reported. Environmental transmission by fomites is rarely, if ever, involved. Human rabies is usually caused by a bite, but it has been acquired by corneal transplantation also. Infections with salivary shedding of virus before obvious clinical signs have been observed, and thus the absence of dramatic neurologic abnormalities cannot be used to rule out absolutely the possibility of rabies infection (Greene, 2006).

Clinical signs in canines

Rabies virus infection has classically been divided into two major types: furious and paralytic. The classification and progression of infection is artificial because rabies can be quite variable in its presentation, and atypical signs are commonly seen. Not all animals progress through all the clinical stages. The initial history may reveal that the pet has a wound history. Because of the severity of wounds, signs may not always be suspected as coming from a bite.

During the prodromal phase, which usually lasts 2 to 3 days, apprehension, nervousness, anxiety, solitude, and variable fever may be noted. Friendly animals may become shy or irritable and may snap, whereas fractious ones may become more docile and affectionate. Pupillary dilation with or without sluggish palpebral or corneal reflexes may become apparent. Most animals will constantly lick the site of viral inoculation. Some dogs may develop pruritus at the site of exposure and claw and chew at the area until it is ulcerated. The behavior of cats during the prodromal period is similar; however, cats more typically show fever spikes and unusual orerratic behavior for only 1 or 2 days. The furious or psychotic type of the disease in dogs usually lasts for 1 to 7 days and is associated with forebrain involvement. Animals become restless and irritable and have increased responses to auditory and visual stimuli. They frequently become excitable, photophobic, and hyperesthetic and bark or snap at imaginary objects. As they become more restless, they begin to roam, usually becoming more irritable and vicious. Dogs may eat unusual objects (pica), especially wood, that become gastrointestinal foreign bodies. They may avoid contact with people and refer to hide in dark or quiet places. When caged or confined, dogs often try to bite or attack their enclosure. They usually develop muscular in-coordination, disorientation, or generalized grand mal seizures during this phase. If they do not die during a seizure, they may experience a short paralytic stage and then die. Cats can develop more consistently the furious phase of the disease, showing erratic and unusual behavior. These cats are described as having anxious, staring, wild, spooky, or blank looks in their eyes. When confined in cages, they may make vicious, striking movements and attempt to bite or scratch at moving objects. In addition, they may have muscular tremors and weakness or in coordination. Some cats may run continuously until they seem to die of exhaustion. The paralytic or dumb type of rabies usually develops within 2 to 4 days (range, 1 to 10 days) after the first clinical signs are noted. LMN paralysis usually progresses from the site of injury until the entire CNS is involved. Cranial nerve paralysis may be the first recognizable clinical syndrome if the bite occurs on the face. When the brain stem becomes affected, a change in the tone of the bark, resulting from laryngeal paralysis, may be observed. Dogs, which more commonly show this type of disease, may begin to salivate or froth excessively as a result of the inability to swallow and the deep labored respiration that occurs. A "dropped jaw" develops as a result of paralysis of the masticatory muscles. Dogs may make a choking sound, which convinces an owner that something is caught in the animal's throat. Owners or veterinarians may then become exposed to the virus in the saliva while attempting to remove a suspected foreign object. The course of the paralytic phase usually lasts 2 to 4 days. The animal often goes into a coma and dies of respiratory failure. The paralytic disease in cats often follows the furious form of the disease and begins around day 5 of clinical illness. Although the total course of illness may last 10 days, rabid cats often die after 3 to 4days. 295As in dogs, initial paralysis of the bitten extremity can progress to paraparesis, in coordination, and ascending or generalized paralysis, terminating in coma and death. Mandibular and laryngeal paralysis is less common in cats. Increased frequency of vocalization is a commonly reported sign in cats, and owners often recognize a change in the pitch of the cat's voice. Cats occasionally develop the paralytic form directly after the prodromal phase with few or no signs of excitement (Greene, 2006).

Diagnosis

Diagnosis of wild animals is problematic for specialists because the initial clinical signs of rabies are non specific. No reliable antemortem methods are available to diagnose rabies during the incubation period. Clinical signs are good indication for rabies in small animals. However rapid and accurate laboratory diagnosis for animal rabies is important for confirmation. In addition, many animals may not show typical signs of rabies. Usually rabid or suspected rabid wild animals are road kill or otherwise deceased when brought into diagnostic laboratories. Laboratory diagnosis is very important because it provides not only data for epidemiological investigation of animal rabies, but also guidance for initiation of PEP in affected people. (CDC, 2003)

Direct florescent antibody assay (dFA)

The most frequently used method for rabies diagnosis in the laboratory is dFA (Dean and Ableseth, 1973; Dean et al. 1966) Usually, brain smears or brain imprints from rabid or suspected rabid animals are reacted with fluoresce in isothiocyanate (FITC)-conjugated-anti-rabies N antibodies (Trimarchi and Debbie, 1972). When observed under a fluorescent microscope, the green-fluorescent foci will show the rabies virus antigen. dFA is rapid, economical, and sensitive for laboratory diagnosis of animal rabies. Rabies antigens can be detected by the specific antibody; however, they should be differentiated from the non-specific background.

Direct rapid immunohistochemistry test (dRIT)

Recently, the CDC developed the dRIT, which is similar to dFA. Brain smears or imprints on glass slides are fixed with 10% buffered formalin. According to standard immunohistochemical staining, the virus antigen can be detected by anti-rabies N monoclonal antibody and examined under a light microscope. The sensitivity and specificity of dRIT is equivalent to that of the dFA. (Lembo et al., 2006)

Virus Isolation

Mouse inoculation is a world health organization (WHO) recommended method to confirm dFA when the result is negative. Usually, brain suspension or spinal fluid from rabid or suspected rabid animals is intracerebrally inoculated into mouse brain. Two mice are killed every 2 days post infection until day 20 and brain smears are subjected to dFA. The 50% mouse intracerebral lethal dose (MICLD50) can be calculated. Virus isolation can also be performed in cell culture, usually on neuroblastoma cells. The 50% tissue culture infective dose (TCID50) can be calculated. Cell culture inoculation is as sensitive as the mouse inoculation test and it requires less time to obtain results (Reed and Muench, 1938; Koprowski, 1973; Webster et al., 1976).

Reverse transcriptase Polymerase chain reaction (RT-PCR)

RT-PCR is a newly developed method for rabies diagnosis. RT-PCR is very useful when sample size is small such as saliva and spinal fluid. Viral RNA is amplified by RT-PCR with primers usually designed from the N gene, the most conserved gene in rabies virus. RT-PCR for rabies diagnosis is as rapid as dFA and is as sensitive as mouse inoculation test. RT-PCR is also widely used in epidemiological investigation and outbreak studies. When combined with sequencing, this method can also be used to differentiate rabies virus variants from multiple species of animals Viral variants can also be differentiated with different monoclonal antibodies in an indirect fluorescent antibody assay (Sacramento et al., 1991).

Histopathology and Immunohistochemistry

Rabies diagnosis in small animals can also be performed on brain tissues by histopathology and immunohistochemistry. Histopathology may show lymphocytic inflammation, perivascular cuffing, gliosis, and neurodegeneration. Inflammation is diffuse in neuraxis. The parenchymal glial response is at first microglial but later mixed with astrocytes. Neurondegeneration is often not severe. The severity of inflammation may vary between animal species. Sometimes, a spongiform encephalopathy with vacuolation in the gray matter can be observed. Negri bodies which are ovoid eosinophilic intracytoplasmic inclusions are a hallmark for rabies diagnosis. Yet Negri bodies are not found in all rabies cases (Butts et al., 1984).

Detection of rabies virus-specific antibodies

Detection of specific antibodies can be used as diagnostic tools for rabies. There are many methods that have been developed to detect rabies-specific antibodies. Rapid fluorescent focus inhibition test (RFFIT) is the method used most often to detect virus neutralizing antibodies. ELISA has also been used to detect virus-specific antibodies when the ELISA plate is coated with rabies virus antigens. Since antibodies take several days to develop, this method is rarely used in diagnosis of animal rabies. Rather detection of virus-specific antibodies is often used in vaccination studies (Budzko et al., 1983; Mebatsion et al., 1989 and Mebatsion et al., 1992).

Control

An effective strategy for preventing rabies consists of controlling rabies in the host reservoir with vaccination. Rabies vaccine has proven to be the most effective weapon for coping with this fatal viral zoonotic disease of warm-blooded animals, including human. The rabies vaccines in use presently protect against many Lyssa viruses with studies showing that it will protect against all known rabies strains (Carter and Wise, 2005). Vaccines have been used successfully against rabies all over the world conferring about 3 years immunity. The threshold immunity is antiboby level of 0.5 IU/mL and above though protection have not been fully equated to antibody response (Wilsmore et al., 2006; WHO, 2010). Animal management is the keystone of any modern programme for the prevention and control of rabies. Historically, "animal control" for local elimination of disease was largely equated with population reduction. However, with relatively few exceptions, culling alone has not led to effective control of rabies. Globally, the greatest burden on human health that is attributable to this zoonosis is caused by uncontrolled rabies in dogs. Where political willingness, biomedical infrastructure, and economic stability permit the sustained use of control measures (e.g. stray animal removal and mandatory parenteral vaccination), rabies has been significantly suppressed and even eliminated over large geographical areas. While control activities have traditionally focused upon certain Carnivora species, bats represent another worldwide rabies reservoir. Indiscriminate killing of bats and destruction of roosts was once the norm, but such activities are not sanctioned by reputable organizations today. Even vampire bats, responsible for substantial effects on health and agricultural losses in the New World (Mexico to Argentina), should be targeted only by specific control applications, rather than by more widespread, unconventional, non-specific methodology. Bats should be excluded from human living quarters. Implementing measures to prevent bats from gaining access to homes should occur at an appropriate time when the bats are absent, especially to avoid sealing the non-flying young within a building. Although great progress has been made during the past four decades in the induction of herd immunity among free-ranging carnivores via oral vaccination against rabies, similar novel solutions have not been readily applied to bat populations. Given these challenges, new paradigm shifts are eagerly anticipated as additional biotechnological applications are developed to deal with domestic animals and wild life. Vaccination of domestic pets and livestock provides an added layer of protection. Finally, oral rabies vaccination (ORV) of wildlife limits and prevents the spread of rabies virus among terrestrial meso-carnivore populations and reduces risks of spill-over infections into domestic animal and human populations (NASPHV, 2016). Prior to ORV development, wildlife rabies control measures consisted largely of eliminating or reducing reservoir wildlife populations through localized and targeted hunting, trapping, (Rosatte et al., 1992). However, these methods became controversial in some areas due to animal rights concerns and perceived negative impacts on biodiversity. Further, these approaches are labor intensive, may only control small-scale outbreaks, and in some instances were ecologically and economically question- able (Aubert, 1994). A more efficient and cost effective wildlife rabies control strategy was needed. Oral immunization of wildlife reservoirs was first considered as a potential approach to rabies control in the 1970s after genetic manipulation of rabies viruses under laboratory conditions yielded less virulent forms. Later biotechnology advances produced a recombinant vaccinia vector expressing the rabies virus glycoprotein gene (Esposito et al., 1987). An international collaboration of scientists leveraged these developments as they searched to find an efficient and cost-effective wildlife rabies control approach in the United States of America (USA) (Baer, 1975) and in Europe (Steck et al., 1982). Early work focused on bait delivery to caged wildlife (Winkler and Baer, 1976) and the first ORV feld trial occurred in October 1978 in Switzerland using an attenuated rabies virus vaccine derived from the Street Alabama Dufferin (SAD) strain inserted in chicken head-baits. Afterwards, large-scale ORV feld trials targeting foxes were conducted in multiple European countries to control endemic fox rabies using a SAD-derived attenuated rabies vaccine ("standard" or SAD-B19 strain) (Wandeler et al., 1988).

Control of rabies in the wild animals reservoir particularly free living is very difficult, since no proper data exist on the immunogenicity and safety of anti rabid vaccines for wild animals, the proper selection of a vaccine is very important

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