Epidemiological and Ecological Perspectives on Kyasanur Forest Disease - A Review

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Abstract

Kyasanur Forest Disease or Monkey fever is a viral zoonotic tick borne disease caused by flavivirus. Route of transmission mainly by the bite of tick *Haemaphysalis spinigera*. These ticks are widely distributed in tropical and deciduous forests of southern and central India. Hence this disease spread along with forest areas. Host range is wide, which includes humans, tick species, rodents and monkeys. This zoonotic disease occurs at the interface of the animal-human interaction, mainly villages nearby forest areas and inter-state borders. People who frequently visit the forest areas like forest guards and officials, range forest officer, hunters, people who handle dead animal carcasses, tribal communities living inside the forest areas and workers working in infected tick areas will have a high risk of getting KFD infection. There are several ecological factors which influence the transmission of disease. Deforestation and reforestation contribute to changes in population dynamics of forest. Which ultimately leads to vector multiplication thereby the transmission of disease. This review is an attempt to give insight of epidemiological and ecological perspective of KFD.

Keywords: Zoonosis, *Haemaphysalis spinigera*, Risk, Deforestation, Ecology, Epidemiology.

1. Introduction

Kyasanur Forest Disease (KFD) is an emerging viral zoonotic, tick borne disease with high infectivity among human and non-human primates. The disease is caused by a KFD virus belonging to the family *Flaviviridae*. It is transmitted to humans through the bite of infected hard ticks, *Haemaphysalis spinigera* which act as a reservoir. There are lots of human cases reporting every year with a morbidity rate of 2-10% in South India (Gould and Solomon, 2008). According to the U.S. Centre for Disease Control and Prevention, there are about 400-500 cases of KFD per year in India and case fatality is about 3-5%. Geographically it is focused in southern states of India, but the area has been expanding in recent years. First case of KFD was reported from forest area of Shimoga district, Karnataka, India among monkey during March, 1957 (Bhatt et al., 1966). During the same period acute febrile haemorrhagic disease in human was also reported (Work et al., 1959). Then KFD spread to nearby states of Karnataka like Maharashtra, Goa, Kerala, Tamil Nadu in short period, which indicates the potential of disease (Awate et al., 2016; Sadanandane et al., 2018). As a tick borne infection, it has a seasonal occurrence from January to June. Monkeys and humans are the only known host species that build up clinical disease with KFD virus. Small mammals like porcupines, squirrels, rodents, shrews and ground birds are also affected in the endemic areas with tick population (Pattanaik et al., 2006). Kyasanur forest disease is endemic in Karnataka, Tamil Nadu and Kerala (CDC, 2013). As prophylactic measure formalin inactivated tissue culture vaccine is used in the diseased areas. In spite of vaccination, every year new cases are reporting from these areas. The emergence of new cases can be due to low vaccine coverage (Kasabi et al., 2013) or due to lack of proper control of tick in endemic areas. Both effect of extensive deforestation to make way for plantations and climatic trends conducive to the viral transmission, which may have led to the development of cases (Ajesh et al., 2017). Clearly, a complex set of processes account for the initial outbreak of KFD among monkeys and subsequent illnesses in humans and recent spread of the virus (Shah et al., 2018).

2. Etiology

KFD is caused by Kyasanur Forest Disease virus (KFDV), which is a positive sense, single stranded RNA virus of the genus *Flavivirus*, family *Flaviviridae* (Thiel et al., 2005). It is spherical (40-65nm in size), enveloped virus with an icosahedral nucleocapsid. The genome of *flavivirus* has 8 non-structural proteins and 3 structural proteins such as Capsid, prM, and Envelop. Cytoplasm is the site of viral replication, where the infected cells utilizing host cell’s polymerase (Kofler et
al., 2006; Villordo and Gamarnik, 2009). There are 2 groups of flaviviruses based on mode of transmission, one is with known vector and the other with unknown vector (Carletti et al., 2010; Memish et al., 2011). Serologic studies and phylogenetic sequencing shows that KFD is a group of tick borne viruses of mammals associated with hemorrhagic fever and is closely related to Alkhurma virus in Saudi Arabia and Egypt (LaSala and Holbrook, 2010). During 1995 and 2001, a novel Flavivirus was isolated from haemorrhagic fever patients in Jeddah and Makkah area of Saudi Arabia (Madani et al., 2011). The genome of KFDV is very similar to that of Alkhurma Hemorrhagic Fever Virus which is primarily found in Saudi Arabia (Dod et al., 2014). Charrel et al. (2007) isolated Alkhurma virus from Ornithodoros savignyi. Another variant of KFDV was isolated from a febrile patient in south western China initially referred as Nanjianyin virus. Later studies grouped the Nanjianyin virus in KFDV group (Wang et al., 2009). The tick born flaviviruses spread is very slow in different geographical areas (Gould et al., 2001; Gould and Solomon, 2008). Diversity and evolution study shows that various isolates of KFDV from India, Saudi Arabia and China share a recent common ancestor (Mehla et al., 2009).

3. Host and Vector

KFDV infection was reported mainly from wild primates and humans. The natural host of KFDV mainly involves wild primates: black faced langurs (Semnopithecus entellus) and red faced bonnet monkeys (Macaca radiata) and various tick species like Haemaphysalis (Pattanaik, 2006). Monkeys are major reservoir hosts and they are often unable to withstand the power of the virus and die shortly after infection (Mourya et al., 2012). Many wild animals like Blanford rat (Rattus blanfordi), striped forest squirrel (Funambulus tristriatus) and the house shrew (Suncus murinus) serve as natural hosts. Sufficient viremic titers for the transmission was found in these animals (Trapido et al., 1959). Cattle also host for the primary vectors, but they do not amplify the virus. Though cattle may act as maintenance hosts (Rajagopalan and Sreenivasan, 1981). Host range is wide, which includes humans, tick species, rodents (shrews, forest rats, white tailed rat, and white bellied rat), monkeys (grey langur, black-faced langur, and bonnet macaque), bats, ground dwelling birds, squirrels, Indian crested porcupines. In experimental infections, high virus titers was noticed in black-napped hares, porcupines, flying squirrels, Malabar giant squirrels, three-striped squirrels, gerbils (Boshell et al., 1969). Domestic ruminants can maintain the infected tick population for long time. Other than larger mammals, many small forest mammals can maintain the virus and have the ability to infect ticks. These include Blanford's rat, jungle striped squirrel, field mice, Indian gerbil, frugivorous and insectivorous bats and the common house shrew (Mourya and Yadav, 2016). The tick Haemaphysalis spinigera act as a major vector for KFD. These ticks are widely distributed in tropical and deciduous forests of southern and central India. KFDV also isolated from various species of ticks like H. turturis, H pauana kinneari, H. kyanusirenensis, H. minuta, Dermacentor, Ixodes. Hyalomma marginatum isacci, Rhicopephalus haemaphysaloides (Sadananade et al., 2018). It is also transmitted by soft ticks of the Ornithodoros genus (Holbrook, 2012; Mourya and Yadav, 2016). Life cycle of H. spinigera completed within 118-160 days under laboratory conditions with a temperature range of 18-35°C (Ghalsasi and Dhandha, 1974). Haemaphysalys species are common ticks in the temperate region, and they infects more than one animal during their life-cycle (Geevarghese et al., 2011). Life cycle of tick consist of major life stages like larvae, nymph and adult. They feeds on three different vertebrate hosts for moultng and nourishing their eggs. At the site of bite, they inject their saliva into the host and virus enters the host along with saliva (Nuttall et al., 2010). Bite and attachment of tick on the host while feeding is painless and extend for a longer duration. Ticks can be infectious only after an infection during their immature larval stage and can be infectious throughout the life by transstadial route (Ajesh et al., 2017). However there was no evidence of transovarial transmission; an ixodid tick can act as a natural reservoir because of longer life span. For primates and humans, nymphs are the more infective life stage of KFD (Shah et al., 2018). The immature ticks are nonspecific in host selection and frequently feeding on all immediately available living-hosts like humans. Hence humans act as an accidental and dead end host, which have no role in the maintenance of virus. Commonly, hard tick separated from dead host and search for others to complete feeding process. Therefore risk is high when entering the closer zone to infected dead monkey were suspected to be infected tick bites and KFD infection (Mourya and Yadav, 2016). Human act as a dead end host in the transmission with no sufficient viremia for further spread. In human incubation period is about 2 to 7 days following the bite from an infected tick. Neutralizing antibodies of virus have been found in cattle, buffaloes, goats, wild boars, porcupines, squirrels, flying squirrels, rats, mice, shrews, bats and a number of bird species. Virus amplification takes place in monkeys (Ajesh et al., 2017). Since monkeys act as sentinel animals for KFD, their deaths can be used as event based surveillance system which helps in application of preventive measures in endemic areas (Murhekar et al., 2015).

4. Risk Factors

The disease was found endemic in different districts of Karnataka, Tamil Nadu and Kerala, Maharashtra and Goa. Along with this related virus was also isolated from Saudi Arabia and China. This zoonotic disease occurs at the interface of the animal-human interaction, mainly villages nearby forest areas
and inter-state borders. People who frequently visit the forest areas of the Western Ghats region like forest guards and officials, range forest officer, forest watchers, shepherds, firewood collectors, dry leaf collectors, hunters, people who handle dead animal carcasses, travellers who camp in the forest areas, tribal communities living inside the forest areas, cashew nut workers and areca nut farm workers working in infected tick areas will have a high risk of getting KFD infection. People who live in the KFD endemic areas and not ready to take KFD vaccination are also at risk. Persons will get the infection by the bite of infective ticks while visiting forest areas for recreation, hunting or for collecting wood and herbs. The seasonal occurrence of disease also reported during dry periods. During this period, the risk of exposure increases while visiting the forest areas without adequate protective measures. The environmental conditions influence tick multiplication, thereby makes an area endemic for KFD (Parola and Raoult, 2001). Nowadays occurrence of tick-transmitted diseases increased around the globe (Piesman and Eisen, 2008; Nicholson et al., 2010). Introduction of ticks to new areas occurs when grazing of cattle in forest area with infected ticks (Chomel et al., 2007). In India, KFD virus is ranked as one of the highest risk categories of pathogens. The virus is also considered as a potential biowarfare agent (Borio L et al., 2002). More than hundred laboratory persons got infected and suffered with the disease during investigative procedures. At the time of investigations, majority of the infections occurred in field while handling on etiological agent, arthropods and mammals in nature.

5. Route of Transmission

During 1950, human population in Shimoga increased which leads to the needs of wood and land for agriculture which results into destruction of local forest areas (Boshell, 1969). Alteration of ecosystem occurred as a result of human intervention may led the way for introduction of virus from its wild reservoir host to humans. All tick-borne Flaviviruses share one general feature in its natural transmission cycle. Man having no role in virus transmission in any of these diseases. Humans do not show sufficient viremia to infect the ticks (Labuda et al., 1993). Rodents are best maintenance hosts; because of their short generation time. In ticks, virus is maintained throughout life, the virus is passed to next generation through trans-stadial and trans-ovarial transmission. Virus transmission among ticks are more when co-feeding of mammalian host takes place as compared with feeding a viremic animal (Randolph, 2011). KFDV was maintained and circulated in small mammals such as rodents, shrews, ground birds and ticks in enzootic areas (Pattnaik, 2006). Infection of wild monkeys occurs through the bite of infected ticks and further spread to other non infected ticks and monkeys. Severe febrile illness was noticed in some of the KFD infected monkeys.

Human’s contract infection mainly through the bite of infected nymph and also by contact with infected animals especially monkeys. Horizontal transmission between humans not reported. Accidental tick bite act as route of transmission among persons visiting forest for recreation or for collecting wood (CDC, 2013). Black-faced langurs were found highly vulnerable to the virus among primate host (Sreenivasan et al., 1986). Tick population peaks during dry season (December to May), which results in epizootics (Rajagopalan et al., 1968). Viremic birds act as carrier of tick infected with virus and also cause distant spread (Gould and Solomon, 2008). The environmental conditions influence the tick multiplication, thereby makes an area endemic for KFD (Parola and Raoult, 2001). In recent years, occurrence of tick transmitted diseases were increased around the globe (Piesman and Eisen, 2008; Nicholson et al., 2010). Introduction of ticks to new areas happens when grazing of cattle in forest areas with infected ticks (Chomel et al., 2007). Inhalation of aerosols may be the most frequent way of acquiring infection between persons handling the infected materials. Other means of transmission includes while conducting post mortem examination, accidental parental inoculation, spilling out of contents from broken glassware or accidental ingestion (Banerjee et al., 1979).

6. Epidemiology

During 1956, large number of monkey mortality were reported followed by acute, febrile haemorrhagic disease in humans in the forest area of Shimoga district Karnataka, India (Work et al., 1959). Research on this leads to the isolation of a new Flavivirus from the autopsied samples from monkeys. Later, an analogous virus was isolated from Ixodid ticks population in the affected forest areas. Kyasanur Forest disease gets its name when the first viral isolate was obtained from Kyasanur forest (Dobler, 2010). Transmission is mainly by the tick of genus Haemaphysalis. Small wild mammals act as natural host of the virus, they become viremic and are infested by various stages of ticks. KFD is endemic in 5 areas of Karnataka, India mainly Shimoga, Chikkamagalore, Uttara Kannada, Dakshina Kannada, and Udupi. Around 500 cases are reporting from these areas in every season of epidemic (Pattnaik, 2006). Outbreaks in human population of Shimoga district, Mysore State were reported from 1959-1966 (Upadhyaya et al., 1975). Similarly reports of non human primates are from 1957-1964 (Goverdhan et al., 1974) and 1964-1973 (Sreenivasan et al., 1986). During 2003, a total of 953 suspected cases were reported from human patients, out of which 306 were confirmed and 132 suspected cases from non human primates and out of that 11 were confirmed as KFD cases from Karnataka. During 2004, out of 568 suspected cases, 153 were confirmed in humans and out of 86 cases reported, 8 were confirmed as KFD in non human primates. From 2005-2008, a total of 1208 cases were
reported from Shimoga district out of which 212 were positive for KFDV in humans. Between 2009 and 2011, a total of 225 suspected cases from humans, 83 were confirmed. From 2003 to 2012, the case fatality rate is around 3.4%. During this period, maximum cases reported in 2003 and the least in 2007 and 2010. During 2003-2012, Case fatality rate of KFD in non human primates is 1.4% (Holbrook, 2012). Among 215 suspected cases from different villages of Shimoga from December 2011-March 2012, 61 were KFD positive (Kasabi et al., 2013). More cases are reported from adult males of those areas. In 2012 from Bandipur National Park, Karnataka, 12 out of 21 suspected cases in humans, 4 monkeys (total death 12) and 2 out of 14 tick pools were confirmed as KFDV positive (Mourya et al., 2012). This study confirmed the spread of KFDV to new foci. Detection of KFDV in Tamil Nadu and Kerala State of India, pointing out the presence of the virus in several tropical forest areas of India. Serological evidences showed that the probable existence of KFDV in different states of India (Pattnaik, 2006). KFDV variants have been isolated from Saudi Arabia and China (Wang et al., 2009). During 1995 and 2001, a novel flavivirus was isolated from haemorrhagic fever patients in Jedda and Makkah area of Saudi Arabia (Madinan, 2005; Alzahrani et al., 2010). This novel flavivirus was initially isolated from Alkhurmi district, Saudi Arabia, hence named as Alkhurma virus infection. Another variant of KFDV was isolated from a febrile patient in south western China initially referred as Nanjianyin virus. Later studies grouped the Nanjianyin virus in KFDV group. Incidences of KFD in monkey were also confirmed in Nilgiris district of Tamilnadu. One incidence of Human was confirmed in Kerala State from Noolpuzha- Aalathoor colony in Wayanad district in 2013. Later in April 2014, the dreaded KFD has been diagnosed among monkeys of the temple compound at Vallikkavu near Chengannur in Kerala's Alappuzha district. Monkey deaths and human cases have now been reported from three neighbouring states bordering Karnataka, i.e., Wayanad (2013) and Malappuram districts of Kerala (2014), North Goa district of Goa state (2015), and Sindhudurg district of Maharashtra (2016) (Mourya et al., 2016). Silent spread of KFD foci also reported by some studies from Andaman and Nicobar Islands (Padbidri et al., 2002), Gujarat's Kutch region (Rao, 1971), parts of West Bengal (Sarkar and Chatterjee, 1962), and areas in Rajasthan (Rao, 1971).

7. Molecular Epidemiology

Unknown variants of KFD virus was identified through different molecular epidemiological studies. Geographically, Alkhurma haemorrhagic fever virus is distributed in Saudi Arabia and Egypt (Carletti et al., 2010; Ravanini et al., 2011; Musso et al., 2015). During 1995, it was isolated from hemorrhagic fever patients of Makkah, Saudi Arabia (Zaki, 1997). Results of Sequence identity of KFDV revealed that 97% with Alkhurma virus, 79.6% with TBEV, 79% with Louping ill virus, 78.7% with Omsk, 78.7% with Langat virus, and 76.3% with Powassan virus. Omsk Hemorrhagic fever virus (OHFV) distantly related to KFDV and which is prevalent in Western Siberia, Russia. Unique members of TBE serocomplex consists of KFDV, AHFV, and OHFV, they cause hemorrhagic fever with neurological implications (Gritsun et al., 2003). Tick-borne flaviviruses have increased during the past few years and were spread from north to west across European and Asian forests. Different Isolates of virus from India and Saudi Arabia share common ancestry despite their wide geographic distribution (Mehla et al., 2009). On the basis of phylogeny, KFD and ALK viruses form some differences from OHF and other viruses within the TBE serocomplex. However, an analysis of the phylogenetic position of KFDV/AHFV and OHFV does not uncover a genetic lineage linked to their hemorrhagic disease producing ability (Lin et al., 2003). Phylogeographic studies of KFDV are also important for genetic characterisation of the recently circulating variants and help to understand the spreading pattern of the virus.

8. Ecological Factors

The spread and persistance of KFD is not clear. The basis for the circulation of the virus and persistent infection of ticks are due to presence of readily available vector competent mammalian reservoirs in the forests (Pattnaik, 2006). The expansion of infected ticks to new areas mainly by the movement of monkeys for searching food (Banerjee, 1988). Deforestation and reforestation contribute to changes in population dynamics of forest. Which ultimately leads to vector multiplication thereby the transmission of disease. Large scale deforestation was reported in Western Ghats during the early 1980s for cashew plantations, which finally leads to largest human outbreak of the disease (Nichter, 1987). KFD is generally found in mountain chain of Western Ghats, which is rich in biodiversity. In the Western Ghats, forest coverage has declined over the past century, from 73.1% in 1920 to 47.1% in 2013 (Reddy et al., 2016). Forest cover has not declined everywhere but in some districts experiencing gains and other districts had losses in forest cover from 1991 to 2017 (Forest Survey of India, 2018). Increase in number of mammalian hosts due to changes in the land use and the spatial overlap with human activity, wildlife and ticks, facilitate efficient and rapid disease outbreak response in the area (Singh et al., 2014). The combination of factors which increase this interaction and lead to higher chances of disease transmission rather than forest coverage (Paul et al., 2016). A decrease in basal hosts in natural environments led to an increase in pathogens specific to a host, thereby increasing the load of the pathogen in the said environment (Morris et al., 2016). Mining operations, plantations, urbanization and fuel wood collection process have huge impact on vector ecology.
and modify human behavior, resulting in increased disease occurrence (Walsh et al., 1993). Potential of KFD increased along with the development of the timber and firewood businesses and encroachment of paddy fields on forested areas (Boshell, 1969). The paddy fields provide suitable habitat for the vector ticks (Pattnaik, 2006). The encroachment of untouched habitats like cashew plantations, search for game meat, activities such as trench digging and fire line works in summer months, dwellings built closer to forest areas and regular entry by villagers and tribal folk dependent on forests have led to more disease occurrence (Gurav et al., 2018; Holbrook, 2012; Murhekar et al., 2015; Patil et al., 2017; Sadanandane et al., 2017). KFDV transmission and the gradual expansion of the disease is also influenced markedly by Population growth. In Shimoga, the increase in human population and the consequent migration into sylvatic areas may have led to humans coming into contact with the infected ticks (Holbrook, 2012). Handling or contact with cattle has been play a role in the transmission cycle of KFD, but the exact mechanism is uncertain. Virus transmission may occur between ticks when they feed on cattle or other mammalian hosts even if the host is not infected (Randolph et al., 1996). Climate change has also been an important factor behind the rising numbers of KFD cases and its gradual expansion. A report from the Indian Ministry of Earth Science during 1951-2010, showed that temperature by state for the entire country found that has increased by 0.60°C (Rathore et al., 2013). Furthermore, increases in annual mean maximum temperature trends in all KFD-affected states were described as "most significant". Precipitation has decreased in all KFD-affected states, with Maharashтра, Goa, Karnataka and Kerala. Most cases of KFD occur during December to May each year following the end of monsoons (Kasabi et al., 2013). Hence changes in the monsoon season may reflect changes in the transmission of KFD as well.

9. Future Perspectives

KFDV is a high risk pathogen, hence biosafety must be considered. Virus and their variants were isolated from India, Saudi Arabia and restricted regions around the world (Mehla et al., 2009). This widespread distribution indicates the massive mobility of the virus (Roy et al., 2017). The disease is spread to newer regions by the movement of rodents and monkeys which maintain the virus. Establishment of incident based surveillance methods for the monkey deaths in endemic areas will help in the early detection of the disease and thereby proper preventive measures can be taken (Murhekar et al., 2015). Disease control is quite difficult because the reservoir mainly exists in the forest. Hence proper understanding of the vectors and their epidemiology is needed for their effective control (Ajesh et al., 17). Incidence of co-infection was reported to be high among ticks and there exists the chances of virus being co-infecting ticks in synergism with other infectious agents (Moutailler et al., 2016). Moreover, control strategy establishment and firm administrative actions against deforestation are required along with other measures (Roy et al., 2017). Organisation of sero-surveys in various districts of the areas will helps in disease mapping (Hollidge et al., 2011). Similarly, for better understanding of evolution mode of virulence in KFDV, further molecular findings are needed (Roy et al., 2017). Rapid eradication of the disease require more organized and large sample studies in the molecular biology of KFDV will help to develop prophylactics and diagnostics methods (Venkatesan et al., 2010). In endemic areas like Karnataka the spread of KFD reduced by using formalin-inactivated tissue culture vaccine. However, the immunity gained through vaccination is short lived and yearly boosters are suggested for about 5 successive years. Efficiency of present vaccine is questionable. In future, main concerns of KFD control consist of effective vaccine with high coverage and long lasting immunity (Hollidge et al., 2011). By considering and understanding all these factors will aid in establishment of newer effective vaccines for KFD and prevention of the infection (Roy et al., 2017). Currently, there is no specific antiviral treatment for humans, hence further options for treatment needs to be assessed for affected individuals (Cook et al., 2016). There are some works on anti-ticks vaccines for preventing multiple tick-borne infections. Selection of suitable antigens to be used for anti-ticks vaccines are based on identification and characterization of tick proteins that involved in feeding and transmission of pathogen (Sprong et al., 2014; Rodríguez-Mallon, 2016). Such vaccines, not only limiting tick feeding and reproduction, but also reduces infection and pathogen transmission from tick to host (Merino et al., 2013).

10. Conclusion

Kyasanur Forest Disease (KFD) is an emerging zoonotic viral tick borne hemorrhagic fever, which is caused by KFD virus (KFDV) belonging to the family Flaviviridae. Haemaphysalis spiniger a tick act as the vector of KFDV, which mainly affect monkeys. KFD in humans presents with high fever, frontal headache, and severe myalgia, followed by bleeding from the nasal cavity, throat, gingivae, and in some cases, gastrointestinal tract. Humans are dead-end hosts of the virus. Every year from South India hundreds of human cases are reporting. KFD in animals is always fatal with an acute onset. Mortality in animals is noticed during the high viremic stage. Diagnosis can be done by virus isolation and antibody based detection methods like hemagglutination inhibition (HI), complement fixation (CF) and neutralization test (NT). Along with this serological and molecular methods can also be used for detection. Prevention strategies such as quarantine, vaccination, early diagnosis, tick control will restrict the entry of virus to new areas. Formalin inactivated tissue culture vaccine are available for immunization in
affected areas. Regular vaccination should be carried out for consecutive five years with increased area coverage. Even though an effective vaccine is available, KFD is still widespread and remain as a source of infection for humans. So effective control strategies are required for prevention.

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