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A REVIEW OF *MONKEY FEVER* - ZOONOTIC VIRAL TICK BORNE DISEASE

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ABSTRACT
Kyasanur Forest Disease (KFD) or Monkey fever is an emerging zoonotic viral tick borne disease affecting mainly monkeys. Every year lots of human cases are reporting with a morbidity rate of around 2–10% in South India. The etiological agent of KFD is Kyasanur Forest Disease virus (KFDV), a RNA virus of the genus *Flavivirus*, family *Flaviviridae*. 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 of genus Haemaphysalis high virus titers was noticed in black–napped hares, porcupines, flying squirrels, Malabargiant squirrels, three–striped squirrels, gerbils. In the transmission of KFDV, human act as a dead end host, with no sufficient viremia for further transmission. Kyasanur forest disease health disease among humans living in and around forests (KFD) is an important public and those whose livelihood depends on forests in certain parts of India.

KEYWORDS: Kyasanur Forest Disease; Monkey fever; RNA virus; wild primates.

INTRODUCTION
Kyasanur forest disease (KFD) a rare viral disease found to be related to the Russian-spring summer virus but differs only because of its hemorrhagic form. KFD is known to be prevalent in the Shimoga District of Karnataka, and it was first identified in the year 1957. Victims of this disease would be those who have been exposed to deceased monkeys in forests or otherwise, have been bitten by an infected tick.[7]

Kyasanur Forest disease virus (KFDV; family Flavi-viridae, genus Flavivirus) was first recognized in 1956 in Shimoga District, Karnataka State, India.[1] The natural cycle of KFDV involves 2 monkey species–black-faced langurs (Semnopithecus entellus) and red- faced bonnet monkeys (Macaca ra- diata)–and various tick species (genus Haemaphysalis). Monkeys become infected with KFDV through the bite of infected ticks; the virus is then transmitted to other ticks feeding on infected monkeys. KFDV infection causes severe febrile illness in some monkeys. When infected monkeys die, ticks drop from the body, thereby generating hot spots of infectious ticks that further spread the virus. In the enzootic state, KFDV circulates through small mammals (e.g., rodents, shrews, ground birds) and ticks.[2] The presence of KFD becomes notice- able when enzootic infections occur and sentinel animals, like monkeys, start dying. Detection of KFDV in Chamarajanagara District, Tamil Nadu State (Nilgiri), and Kerala State indicates the presence of the virus in many evergreen and semi-evergreen forest areas of India. Infections in these areas may have been missed previously because of the lack of an organized surveillance system.[3] The replication of Flaviviruses takes place in the cytoplasm of infected cells utilizing host cell's polymerase.[8]

EPIDEMOLOGY

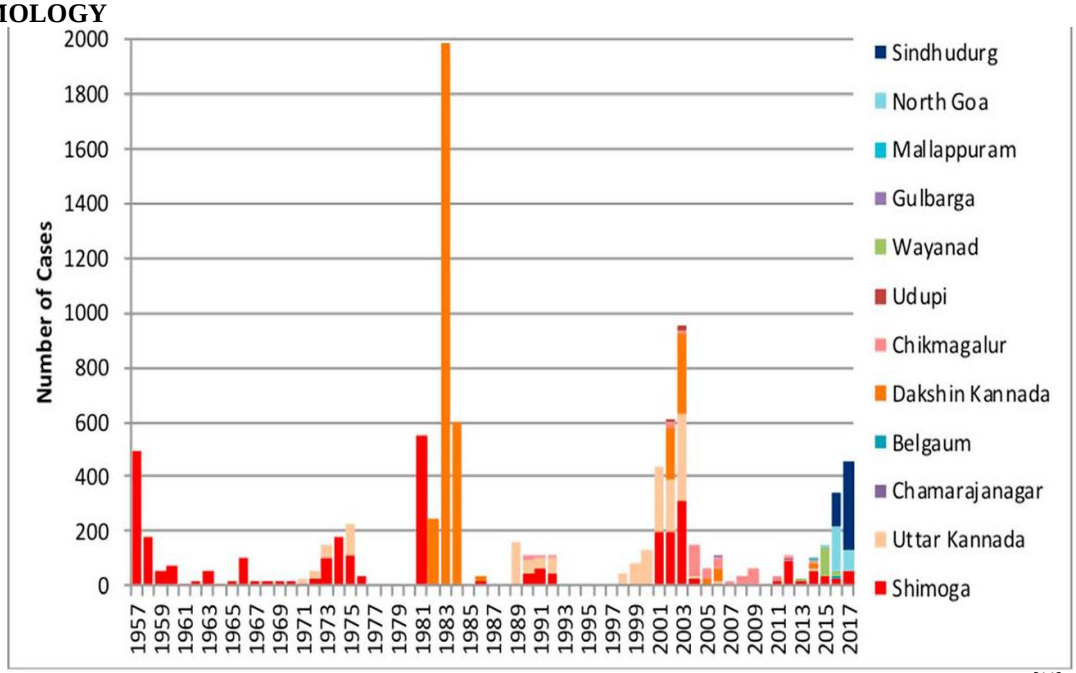
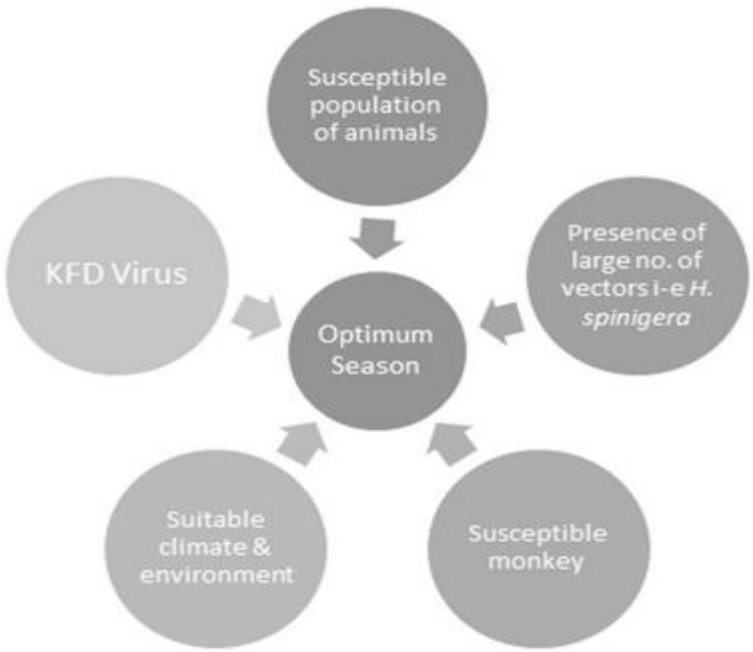


Figure 2: Distribution of Kyasanur Forest disease cases by districts in India (1957–2017).[11]

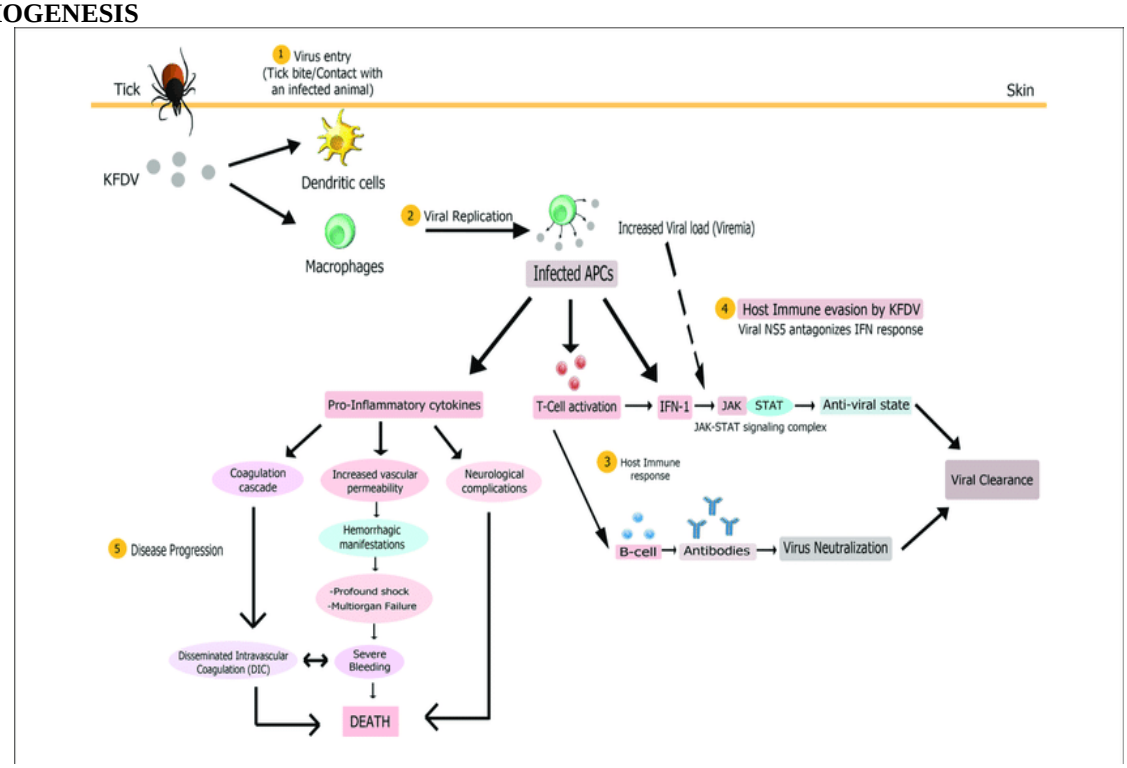
SIGNS & SYMPTOMS

The disease is characterized by a high fever with frontal headaches, followed by hemorrhagic symptoms such as bleeding from the nasal cavity, throat, gums, and gastroin- testinal bleeding. A suspected KFD case was defined as any person with the history of fever with one or more symptoms: head- ache, body ache, myalgia, vomiting, diarrhea, skin rash, any hemorrhagic manifestation, neurological symptoms, and living in villages in a forest For screening of IgM antibodies from suspected.



The confluence of factors responsible for Kyasanur Forest disease (KFD). All of these factors when present in right proportions result in an optimum season for the development of KFD.[9]

PATHOGENESIS



Proposed pathogenesis model of Kyasanur Forest Disease:

Virus enters (1) in body on tick bite or through contact with an infected animal. Virus initially targets macrophages and dendritic cells. Multiplication of virus (2) in these host cells yields high viremia, leading to systemic spread of the virus to spleen, liver, and other replication sites to produce disease symptoms. The infected antigen presenting cells (APCs), that present viral antigens to T cells, could release large amounts of pro-inflammatory cytokines early after infection and also modulate host immune response (3) via type 1 interferon production. Antigen positive (activated) T cells could also produce IFN-1. Subsequent activation of the JAK-STAT signaling induces an antiviral state for alleviating virus burden. Humoral immune response via production of antibodies by activated B cells might also assist in viral clearance from the body. To counter the host immune response, KFDV employs its NS5 non-structural protein to antagonize IFN response (4) by inhibiting JAK-STAT pathway, possibly bringing about uncontrolled viral replication and poor immune response. The multi-systemic illness might be attributed to the pro-inflammatory cytokine storm that could contribute to immunosuppression and disease progression (5) by inducing disseminated intravascular coagulation (DIC), neurological complications and vascular dysfunction that leads to hemorrhagic manifestations, multi-organ failure and shock. These complications altogether finally result in death.[9]

DIAGNOSIS

KFD cases, serum samples were tested by an indigenously developed Anti-KFD IgM ELISA using the inactivated KFDV antigen and biotinylated antibodies as per protocol.[4] Haemorrhagic fevers are contracted through contact with the blood of infected animals, and the bite of infected ticks (CCHF and KFD) and mosquitoes (dengue fever). Some of these fevers can be transmitted from person to person. Laboratory diagnosis of the disease is established by molecular methods, while IgM and IgG antibodies become detectable by indirect immunofluorescence assay or ELISA after the fifth day. However, there are reports that in severe cases no antibody response is observed. Real-time RT-PCR for rapid diagnosis of CCHFV infections is the test of choice in the acute phase, and for ticks. The isolation of CCHFV requires a high-containment BSL-4 laboratory, while viral RNA detection combined with serology for laboratory diagnosis in BSL-3- or BSL-2-compliant laboratories can be carried out following good microbiological practices with standard protocol.[10]

POST -MORTEM FINDINGS

Post-mortem findings of Kyasanur forest disease (KFD) patients Gross and microscopic autopsy findings of KFD cases have shown non-specific disease process. Post-mortem findings revealed predominance and flooding of macrophages and lymphocytes in the liver, spleen and kidney with features of parenchymal disease. Focal necrosis of liver and tubular damage in kidney were the persistent findings. Some cases have shown haemorrhagic pneumonia. Among fatal cases with neurological features, aseptic meningitis-like picture was noted with no specific lesions of meningitis, encephalitis or meningoencephalitis. Abnormalitiesrelated to cerebrospinal fluid (CSF) were also not observed. Very few cases presented with cerebral oedema and

inflammatory cells in the brain tissue. Biochemical and haematological findings A study for biochemical and haematological findings on 26 KFD patients revealed that blood counts were on the lower side (leucopenia, eosinopenia with lymphopenia) during the first week of illness Features of marked leucopenia were common amongst all the cases. Lymphocytosis was observed in the fourth week of illness typical of viral infection. Eosinophilia (3/26 cases), atypical lymphocytes with irregular nuclei (9/26 cases) and atypical monocytes including vacuolated cytoplasm (3/26 cases) were found in the peripheral blood with features of thrombocytopenia Urine may show presence of granular casts, red blood cells and proteinuria. Deranged liver functions with reduced serum albumin and increased levels of alkaline phosphatase, bilirubin and gamma globulin were noted. The renal function tests including serum urea and creatinine were found to be normal. Laboratory diagnosis Earlier laboratory tests for diagnosis of KFD included conventional tests such as virus isolation by in vivo inoculation of serum from patients into suckling mice, serological tests such as haemagglutination inhibition, complement fixation and neutralization test. All these tests were labour intensive and time-consuming. KFDV is ranked as one of the high-risk categories of pathogens belonging to Biosafety Level-4. However, numerous infections in field and laboratory personnel, in the early years following identification of this virus, resulted in suspension of work, until an appropriate Biosafety Level-3 laboratory was fully functional in 200623. This was followed by the development of sensitive diagnostic approaches for identification of KFDV, including nested polymerase chain reaction (PCR) and real-time PCR. IgM and IgG ELISA were also developed and validated. These tests have contributed immensely to the early identification of KFD.[5]

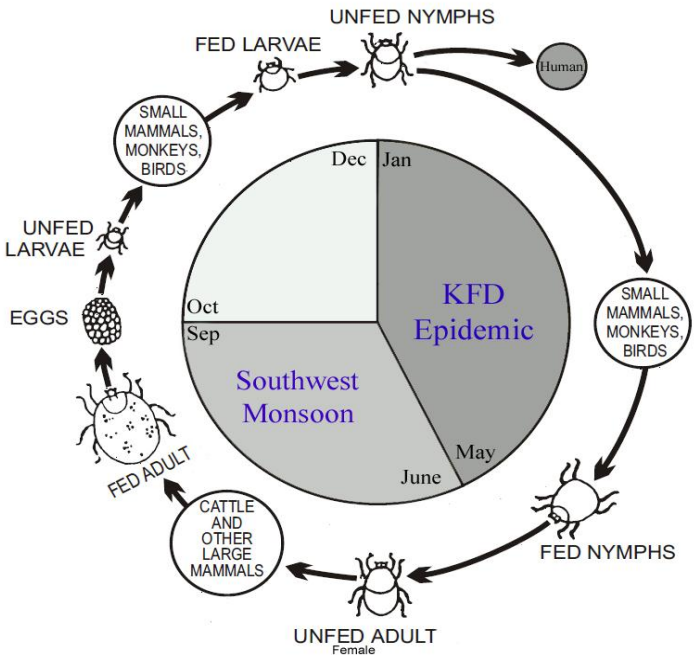


Image 2: Life cycle of KFDV vector tick, Haemaphysalis spinigera. Image is modified from ICMR publication*.[6]

RISK OF EXPOSURE

The KFD was found endemic in various districts of Karnataka, Tamil Nadu and Kerala. Additionally related KFDV was isolated from Saudi Arabia and China. Persons will get bite from infective ticks while visiting forest areas in Karnataka for recreation, hunting or for collecting wood and herbs. The disease has a seasonal occurrence mainly during dry periods (November– June). Visiting the forest areas of Karnataka during this period without adequate protective measures increases the risk of exposure.[8]

TREATMENT

There is no specific treatment for KFD, but early hospitalisation and supportive therapy such as maintenance of hydration and management of neurological symptoms may help control bleeding disorders and complications.[1]

PREVENTION AND CONTROL

Tick borne diseases are emerging as a result of changes in public health policy, acaricide resistance, climatic changes, and emergence of new variant of pathogen. Measures need to be taken for reversal of these conditions. Prevention strategies such as quarantine, vaccination, early diagnosis, tick control will restrict the entry of virus to new areas.

The KFDV has been classified as risk group IV pathogen. Vaccination is one of the main control

strategies for KFD. Formalin inactivated tissue culture vaccines are available for immunization against KFDV in endemic areas. Other control strategy includes wearing protective clothing while handling infectious materials and tick control. Strictly prohibit the visit to affected forest areas during outbreak time. If visit is inevitable, use protective clothing's and gum boots to cover the whole body and apply some insect repellent to exposed body part. The concept of 'one world, one health and one medicine' should be kept in mind while combating zoonotic infections.[8]

VACCINES

An inactivated/killed tissue culture vaccine has been used in endemic areas of Karnataka, India since 1990. Initially 2 doses were used in persons of 7– 65 years of age, in an interval of 4 weeks. Revaccination is required after 6–9 months for five years (Kasabi et al., 2013). Before introduction of formalin inactivated tissue culture vaccine, several other live and inactivated vaccines prepared in tissue culture, formalin–inactivated Russian Spring Summer Encephalitis (RSSE) virus (Aniker et al., 1962; Shah et al., 1962) and mouse brain were used in control programs (Bhatt and Anderson, 1971; Upadhyaya et al., 1979). Incidence of KFD has been reported even in vaccinated individuals. The main drawback of these vaccines is poor area coverage, not taking boosters and poor storage conditions. Utilizing new technologies of vaccine production, develop better vaccine will combat the infection (Dhama et al., 2008; Paul–Pierre, 2009; Dhama et al., 2013c).

Vaccines against KFDV were initially produced in Shimoga district of Karnataka. Later, the unit was moved to Bangalore (Institute of Animal Husbandry and Veterinary Biologicals, Hebbal). In a study conducted by Kasabi et al, (2013) noticed low coverage of vaccine in affected areas even less than half of the target population and the efficiency of vaccine was around 62% in individuals received initial 2 doses and 83% in individuals who received further boosters. In earlier studies, reported the efficiency around 79% in persons with one dose and 94% in those received 2 doses (Dandawate et al., 1994) and about 59% in those have 2 doses during 1970–1971 (Upadhyaya et al., 1979, Dandawate et al., 1980).[8]

CONCLUSION

Kyasanur forest disease (KFD) or Monkey fever is an emerging viral disease. In depth study on pathogenesis is very much important and necessary as it will pave the way for the development of better preventive and therapeutic approaches to counter KFD. More molecular studies are needed to understand the mechanism of evolution of virulence in KFDV. Such understanding will go a long way towards development of more efficacious KFD vaccines and control of the disease.

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