A REVIEW ON: KYASANUR FOREST DISEASE

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Summary

The disease was first reported from Kyasanur Forest of Karnataka in India and manifested as an epizootic outbreak among monkeys killing, hence the disease is also known as Monkey Disease. KFD caused by Kyasanur Forest Disease Virus, a member of the tick-borne encephalitis virus serocomplex of the genus Flavivirus, family Flaviviridae, can cause fever, hemorrhage, and encephalitis. The reservoir hosts for the disease are porcupines, rats and mice. The vector for disease transmission is Haemaphysalis spinigera, a forest tick. Humans contract infection from the bite of nymphs of the tick .Hemorrhage is typically present in many organs, and effusions are common in serous cavities. Widespread necrosis generally occurs, may be present in any organ system, and varies from modest and focal to massive in extent. Liver and lymphoid systems are usually extensively involved, and the lung regularly demonstrates varying degrees of interstitial pneumonitis, diffuse alveolar damage, and hemorrhage. Acute tubular necrosis and microvascular thrombosis may also be observed. The diagnosis is made by virus isolation from blood or by serologic testing using enzyme-linked immunosorbent serologic assay (ELISA). Laboratory tests include Hemagglutination inhibition, immunofluroscence and neutralization test. Prophylaxis by vaccination, as well as preventive measures like protective clothing, tick control, and mosquito control are advised. One or two treatment of forest floor with the insecticide lindane would be highly effective in killing ticks. An attenuated live vaccine is now available for control of the disease.

Keywords: Kyasanur Forest disease, tick-borne encephalitis, ELISA

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Introduction

Kyasanur Forest disease (KFD) is tick-borne hemorrhagic fever endemic to south Asia. KFD caused by Kyasanur Forest Disease Virus, a member of the tick-borne encephalitis virus serocomplex of the genus Flavivirus, family Flaviviridae, can cause fever, hemorrhage, and encephalitis and has a 3%–5% case-fatality ratio. KFD was discovered in 1957 in the Mysore forest region of south India, where 400–500 persons per year were infected with the virus. KFD virus has been found only in monkeys, humans, and Haemaphysalis spinigera ticks in the KFD-epidemic region of south India, although a variant of KFD virus, Alkhurma virus, was isolated recently in Saudi Arabia. The gene sequence of a Nanjianyin virus isolate obtained from a febrile patient was highly homologous to that of KFD virus. The Nanjianyin virus was isolated in 1989 from the serum of a 38-year-old woman from the Hengduan Mountain region of Yunnan Province, People's Republic of China, where a previous serosurvey demonstrated that KFD exposure had occurred.[1]

History [2]

1957	The disease was first reported from Kyasanur Forest of Karnataka in India. The disease was first manifested as an epizootic outbreak among monkeys killing, hence the disease is also known as Monkey Disease.
1999	Kyasanur Forest Disease epidemic diseases, started out as zoonotic diseases. Have increased virulence in populations lacking immunity. Appeared in the United States in the New York City area.
1999	In peninsular Malaysia when intensive pig farming intruded into the natural habitat of fruit bats carrying the virus. Unidentified spillover events caused infection of the pig population which acted as an amplifier host, eventually transmitting the virus to farmers and resulting in 105 human deaths.
2002	Disease moved through the United States country in the summer, causing much distress.

Table 1: History of Kyasanur Forest disease

Outbreaks

Outbreaks of zoonosis have been traced to human interaction with and exposure to animals at fairs, petting zoos, and in other settings. In 2005, the Centers for Disease Control and Prevention issued an updated list of recommendations for preventing zoonosis transmission in public settings.[3] The recommendations, which were developed in conjunction with the National Association of State Public Health Veterinarians, include sections on the educational responsibilities of venue operators, managing public and animal contact, and animal care and management. In 1988, a person became ill with swine influenza virus (swine flu) and died after visiting the display area of the pig barn at a Wisconsin county fair. Three healthcare personnel treating the case patient also developed flu-like illness with laboratory evidence of swine influenza virus infection. Investigators from the indicated in their final report that the swine flu had been transmitted directly from pig to human host.[3]

1988	A person became ill with swine influenza virus (swine flu) and died after visiting the display area of the pig barn at a Wisconsin county fair. Three healthcare personnel treating the case patient also developed flu-like illness with laboratory evidence of swine influenza virus infection. Investigators from the indicated in their final report that the swine flu had been transmitted directly from pig to human host.[4]
1994	Seven cases of E. coli O157:H7 infection was traced to a farm in Leicestershire, United Kingdom. An epidemiological investigation into the outbreak revealed that the strain of E. coli O157:H7 isolated from nine animals on the farm was indistinguishable from the strain isolated from human samples. Investigators concluded that the most likely cause of this outbreak was direct human contact with animals.[5]
1995	Seven cases of E. coli O157:H7 infection was traced to a farm in Leicestershire, United Kingdom. An epidemiological investigation into the outbreak revealed that the strain of E. coli O157:H7 isolated from nine animals on the farm was indistinguishable from the strain isolated from human samples. Investigators concluded that the most likely cause of this outbreak was direct human contact with animals.[6]
1995	43 children who had visited a rural farm in Wales became ill with Cryptosporidiosis. ''Cryptosporidium'' was isolated from seven of the ill children. An epidemiological investigation indicated that the source of the children's illness was contact with calves at the farm.[7]
1995	Least 13 children became ill with Cryptosporidiosis after visiting a farm in Dublin, Ireland. In a case-control study, researchers compared the activities of the 13 ill children, or cases, to the activities of 52 out of 55 people who had visited the farm – the controls. The study revealed that illness was significantly associated with playing in the sand in a picnic area beside a stream where animals had access.[8]
1997	An E. coli O157:H7 outbreak was identified among one child who lived on an open farm and two children who visited the farm during school parties. Two of the three children developed hemolytic-uremic syndrome (HUS). Isolates collected from the three children and from samples taken at the farm were indistinguishable, demonstrating evidence of the link between the farm and the children's illness.[9]
1999	What is believed to be the largest outbreak of waterborne E. coli O157:H7 illness in United States history occurred at the Washington County, New York fair. The New York State Department of Health identified 781 individuals who were suspected of being infected with either E. coli O157:H7 or Campylobacter jejuni. An investigation into the outbreak revealed that consumption of beverages purchased from vendors supplied with water drawn from unchlorinated fairgrounds well was associated with illness. In all, 127 outbreak victims were confirmed ill with E. coli O157:H7 infections; 71 were hospitalized, 14 developed HUS, and two died.[10]
2000	51 people became ill with confirmed or suspected E. coli O157:H7 infections after visiting a dairy farm in Pennsylvania. Eight children developed HUS. A case-control study among visitors to the dairy was conducted jointly by the CDC, Pennsylvania Department of Health, and the Montgomery County Health Department. The study's authors concluded that E. coli was transmitted to visitors as a result of contamination on animal hides and in the environment.[11]

2000	43 visitors to the Medina County fair in Ohio were confirmed ill with E. coli O157:H7 infections. An investigation into the outbreak suggested that the water system from which food vendors were supplied was the source of the E. coli outbreak. Several months later, five children became ill with E. coli infections after attending a "Carnival of Horrors" event held at the Medina County fairgrounds. PFGE analysis of the strains of E. coli isolated from members of both outbreaks revealed an indistinguishable pattern, and investigators from the Medina County Health Department and the CDC determined that the Medina County Fairgrounds water distribution system was the source of both E. coli outbreaks.[12]
2001	An E. coli O157:H7 outbreak was traced to exposure in the Cow Palace at the Lorain County Fair in Ohio. CDC investigators identified 23 cases of E. coli infection associated with attendance at the Lorain County Fair, with additional secondary cases likely. Two people developed HUS. An environmental and site investigation revealed E. coli contamination on doorways, rails, bleachers, and sawdust. Investigators concluded that the Lorain County Fair was the source of the outbreak.[13]
2002	Seven people became ill with E. coli O157:H7 infections after visiting a large agricultural fair in Ontario, Canada. Outbreak investigators conducted a case-control study, which indicated that goats and sheep from a petting zoo were the source of the E. coli among fair visitors. Other indications were that the fencing and environment surrounding the petting zoo could have been a source of transmission. [14]
2003	A large E. coli O157:H7 outbreak occurred among visitors at the 2004 North Carolina State Fair. During its investigation into the outbreak, the North Carolina Department of Health and Human Services (NCDHHS) received over 180 reports of illness, and documented 33 culture-confirmed cases of E. coli O157:H7 associated with attendance at the fair, with 15 children developing HUS. In its final investigation report, NCDHHS concluded that the North Carolina State Fair E. coli outbreak had originated at a petting zoo exhibit. The conclusion was supported by a case-control study, environmental sampling, and laboratory analysis of samples collected from the fair and members of the outbreak.[15]
2004	A large E. coli O157:H7 outbreak occurred among visitors at the 2004 North Carolina State Fair. During its investigation into the outbreak, the North Carolina Department of Health and Human Services (NCDHHS) received over 180 reports of illness, and documented 33 culture-confirmed cases of E. coli O157:H7 associated with attendance at the fair, with 15 children developing HUS. In its final investigation report, NCDHHS concluded that the North Carolina State Fair E. coli outbreak had originated at a petting zoo exhibit. The conclusion was supported by a case-control study, environmental sampling, and laboratory analysis of samples collected from the fair and members of the outbreak.[16]
2005	A petting zoo that exhibited at two Florida fairs and a festival was traced as the source of an E. coli O157:H7 outbreak. Sixty-three people who had visited either the Florida State Fair, the Central Florida Fair, or the Florida Strawberry Festival reported illness to investigators for the Florida Department of Health, including 20 who were culture-confirmed and 7 with HUS. A case-control study revealed that illness was associated with exposure to a petting zoo exhibit present at all three events. [17]

Table 2: Outbreaks of Kyasanur Forest disease

Epidemiology

Kyasanur forest disease (KFD) was first recognized as a febrile illness in the Shimoga district of Karnataka state of India. The causative agent, KFD virus (KFDV), is a highly pathogenic member in the family Flaviviridae, producing a haemorrhagic disease in infected human beings. KFD is a zoonotic disease and has so far been localized only in a southern part of India. The exact cause of its emergence in the mid 1950s is not known. A variant of KFDV characterized serologically and genetically as Alkhurma haemorrhagic fever virus (AHFV), has been recently identified in Saudi Arabia. KFDV and AHFV share 89% sequence homology, suggesting common ancestral origin. Homology modelling of KFDV envelope (E) protein exhibited a structure similar to those of other flaviviruses, suggesting a common mechanism of virus-cell fusion. The possible mechanism of receptor-ligand
interaction involved in infection by KFDV may resemble that of other flavivirses. Present understanding is that KFDV may be persisting silently in several regions of India and that antigenic and structural differences from other tick borne viruses may be related to the unique host specificity and pathogenicity of KFDV. From January 1999 through January 2005, an increasing number of KFD cases have been detected in Karnataka state of Indian subcontinent despite routine vaccination, suggesting insufficient efficacy of the current vaccine protocol. However, the exact cause of the increase of KFD cases needs further investigation. Considering the requirement of safer and more effective vaccines in general, there is clearly a need for developing an alternative vaccine as well as a rapid diagnostic system for KFD. The changing ecology of the prime focus of the KFD also warrants attention, as it may lead to establishment of the disease in newer localities, never reported before. [18]

Virus

Kyasanur forest disease virus
Group: Group IV ((+) ssRNA)

Family: Flaviviridae

Genus: Flavivirus

Species: Kyasanur forest disease virus[19]

The causal agent, EEE, was first isolated from infected horse brains in 1933. In 1938, the first confirmed human cases were identified when thirty children died of encephalitis in northeastern USA. These cases coincided with outbreaks in horses in the same regions. The fatality rate in humans is 35% and there is currently no cure for human infections. [19]

Life Cycle

EEE is capable of infecting a wide range of animals including mammals, birds, reptiles and amphibians. The virus is maintained in nature through a bird - mosquito cycle. There are two mosquito species primarily involved in this portion of the cycle; they are Culiseta melanura and Cs. morsitans. These mosquitoes feed on the blood of birds. The amount of virus found in nature increases throughout the summer as more birds and more mosquitoes become infected. Transmission of EEEV to mammals occurs via other mosquitoes. These other mosquitoes are called bridge vectors because they bring the virus from avian populations to mammalian populations. They include Coquiletidia perturbans, Aedes vexans, Ochlerotatus sollicitans and Oc. canadensis. All these mosquitoes are primarily mammalian feeders. Generally, people only become sick through the bite of an infected mosquito. Humans, horses and other infected mammals do not circulate enough viruses in their blood to infect additional mosquitoes.

There have been some cases where EEEV has been contracted through lab exposures or from exposure of the eyes, lungs or skin wounds to brain or spinal cord matter from infected animals.[19]

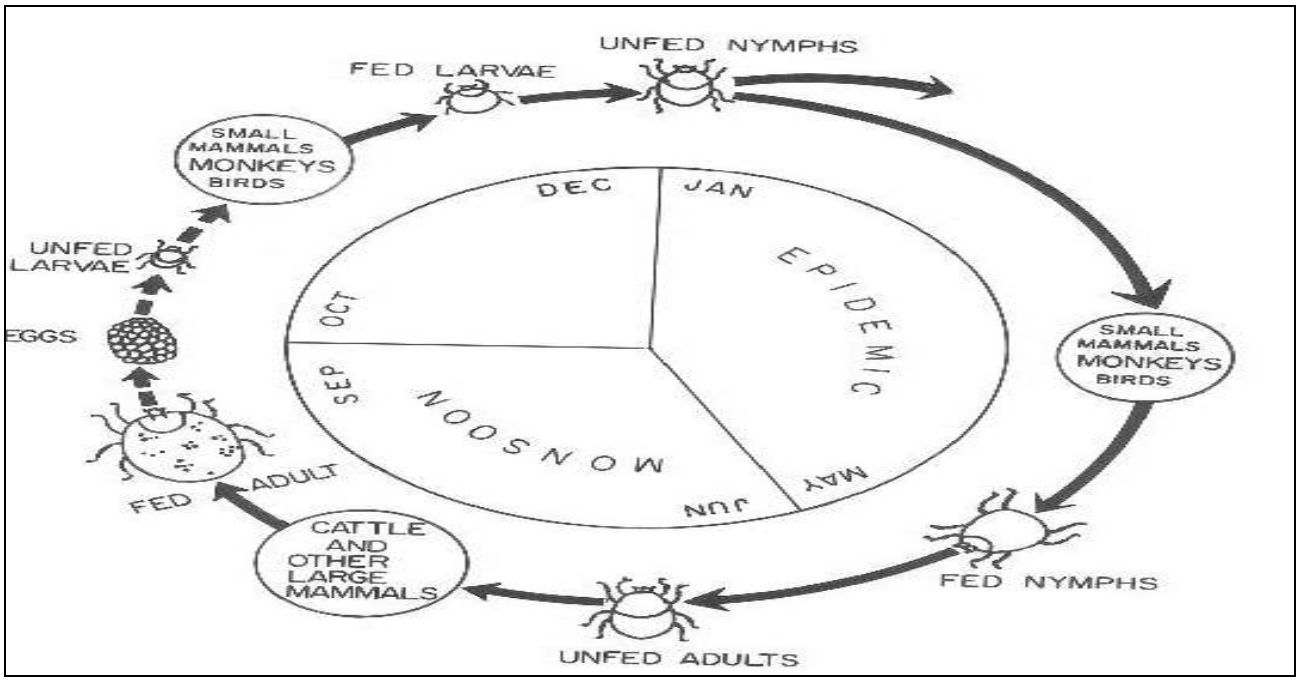

Figure1: Kyasanur forest virus Life cycle

Distribution of KFD in India

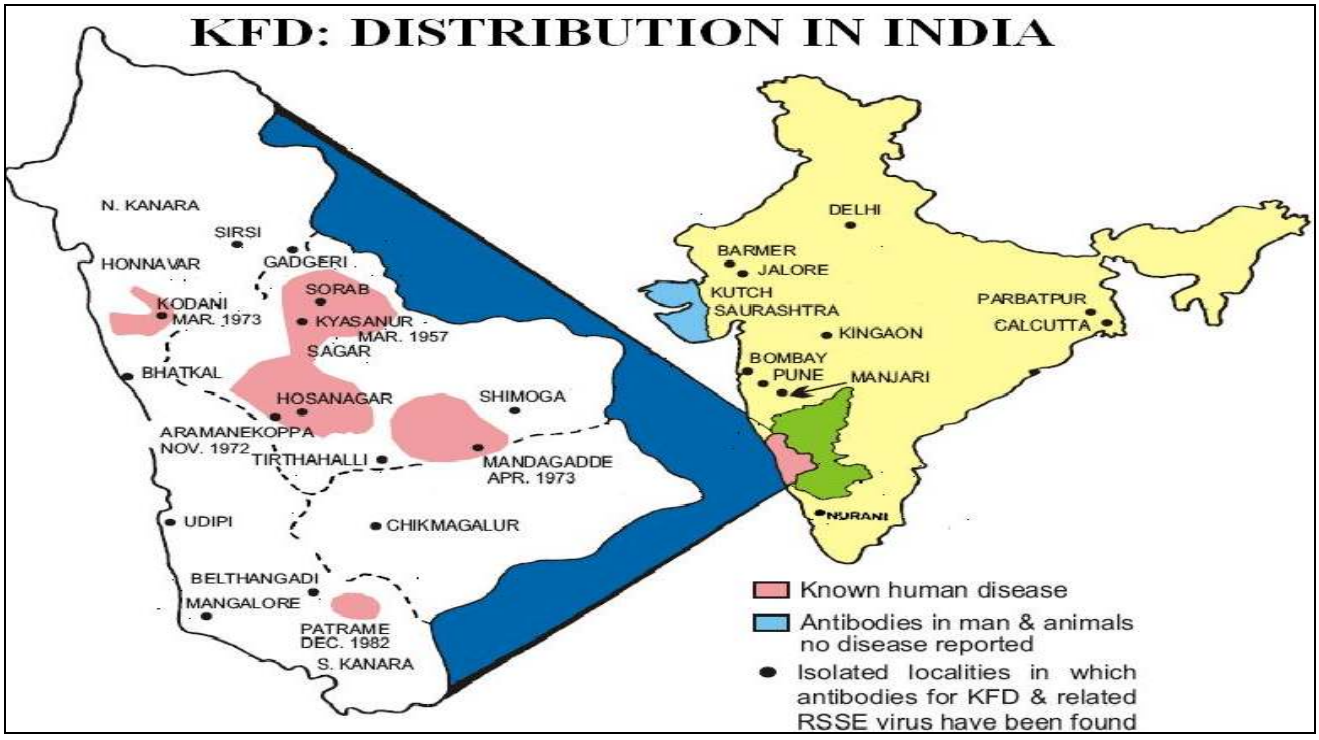

Figure 2: Distribution in India

List of Carriers [21]

Assassin bugs	Hamsters	Rodents
Bats	Horses	Sloths
Bank voles	Humans	Sheep
Birds	Lice	Snails
Cats	Mice	Ticks
Cattle	Monkeys	Fleas
Chimpanzees	Mosquitos	Flies
Dogs	Opossums	Geese
Fish	Pigs	Goats
Raccoons	Rabbits and hares	Rats

Table 3: List of Carriers

Incubation

The reservoir hosts for the disease are porcupines, rats and mice. The vector for disease transmission is Haemaphysalis spinigera, a forest tick. Humans contract infection from the bite of nymphs of the tick. [22]

Species	Incubation period	Clinical signs
Humans	3-8 days	Biphasic course of illness and fever. Sudden onset of fever and headache, back pain, prostration. After a febrile period of 1-2 weeks, CNS symptoms begin to develop; a mild meningoencephalitis frequently occurs. A small proportion of patients develop coma or bronchopneumonia prior to death. 2-10% fatality. [23]
Cattle, sheep, goats		KFD-specific antibody titers can be present but not considered.
Grey langur (Presbytis entellus)	--------	----------
Bonnet macaque (Macaca radiata)	After experimental infection, diarrhea at 4dpi; death by 7dpi	Diarrhea, dehydration, lymphopenia, death.

Rats: Ratus rattus wroughtoni R. blandfordi	No disease	After experimental infection, R. r. wroughtoni, R. blandfordi exhibited low viral titers, no morbidity or mortality
Mice: Mus booduga Vandeleuria oleracea	--------	--------
Palm Squirrel Funambulus tristriatus numarius	2-4 days after experimental infection	Disseminated nonsuppurative encephalitis, death.
Shrew: Suncus murinus	--------	--------

Table 4: Incubation of KFV

Kyasanur Forest Disease Fatality Rate

There are approximately 400-500 cases of KFD per year with a case fatality rate of 3% to 5%.[24]

Symptoms

The disease has a high morbidity rate of 10 %.
The clinical manifestations of the disease in humans are:

- High fever
- Headache
- Haemorrhages from nasal cavity and throat
- Vomiting

An affected person may recover in two weeks time, but the convalescent period is typically very long, lasting for several months. There will be muscle aches and weakness during this period and the affected person is unable to engage in physical activities. [25]

Pathophysiology

Kyasanur forest disease is the Tick borne Hemorrhage fever. Although common themes occur, the different viruses display variable Pathophysiology. Hemorrhage is typically present in many organs, and effusions are common in serous cavities (although they may be minimal or absent in some patients). Widespread necrosis generally occurs, may be present in any organ system, and varies from modest and focal to massive in extent. Liver and lymphoid systems are usually extensively involved, and the lung regularly demonstrates varying degrees of interstitial pneumonitis, diffuse alveolar damage, and hemorrhage. Acute tubular necrosis and micro vascular thrombosis may also be observed. The inflammatory response is usually minimal. The target organ is the vascular bed. Dominant clinical features are due to microvascular damage and changes in vascular permeability. In most cases of viral hemorrhagic fever, the coagulopathy is multifactorial, including: hepatic damage, disseminated intravascular coagulation, primary marrow injury to megakaryocytes.[26]

Diagnosis

The diagnosis is made by virus isolation from blood or by serologic testing using enzyme-linked immunosorbent serologic assay (ELISA). Diagnosis is mainly syndromic. Laboratory tests include Hemagglutination inhibition, immunofluroscence and neutralization test.[26]

Prevention and treatment

Prophylaxis by vaccination, as well as preventive measures like protective clothing, tick control, and mosquito control are advised. An attenuated live vaccine is now available. Specific treatments are not available.

- A timely supportive therapy reduces the mortality rate in humans.
- One or two treatment of forest floor with the insecticide lindane was highly effective in killing ticks.
- This was particularly useful to clear infection following detection of monkey deaths.
- Tick repellent such as DEET, DMP, DBP provide 90-100% protection against tick bite.
- Vaccination of villagers and forest workers is effective.[26]

Vaccination

NIV has developed an inactivated chick embryo tissue culture vaccine against KFD. This vaccine evokes neutralizing antibodies response in about 70% of the vaccinated persons. The technology has been transferred to the Karnataka public Health department for production and vaccination. [25, 26]

Conclusion

Kyasanur Forest Disease Virus, a member of the tick-borne encephalitis virus serocomplex of the genus Flavivirus, can cause fever, hemorrhage, and encephalitis. Considering the requirement of safer and more effective vaccines in general, there is clearly a need for developing an alternative vaccine as well as a rapid diagnostic system for KFD. Recently NIV has developed an inactivated chick embryo tissue culture vaccine against KFD. An affected person may recover in two weeks time, but the convalescent period is typically very long, lasting for several months. There will be muscle aches and weakness during this period and the affected person is unable to engage in physical activities. Prophylaxis by vaccination, as well as preventive measures like protective clothing, tick control, and mosquito control are advised. One or two treatment of forest floor with the insecticide lindane would be highly effective in killing ticks.

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