Chapter 1

Introduction and exposition to the problem
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Introduction

Kyasanur Forest disease (KFD) was first recognized in March 1955 in the forested areas of Shimoga district, Karnataka State, on account of heavy mortality in two species of monkeys; viz. the black faced langur (*Presbytis entellus*) and the red-faced bonnet monkey (*Macaca radiata*). The mortality in monkeys was followed by high incidence of acute prostrating human febrile illness among villagers in the neighbourhood, a small proportion of which ended fatally. Subsequent investigations resulted in the isolation of virus from monkeys, man and ticks. It was named as KFD virus after the forest area where the virus was first discovered. The virus is antigenically related to Russian spring-summer encephalitis and Omsk hemorrhagic fever viruses of the tick-borne encephalitis virus complex (Work and Trapido, 1957). The disease occurs among people who visit the forests for various purposes, particularly villagers who visited the forest for collecting firewood, grass and other forest products. Clinical cases of KFD have so far been reported only from Shimoga, Chikmagalur, South Kanara and North Kanara districts of Karnataka state and within these districts the activity of the virus is found in evergreen, semi-evergreen forest and neighboring moist deciduous forest areas. In the initial stage of discovery, the known activity of the virus was limited to the area bordering Sagar and Sorab taluks of Shimoga district only.

In man the disease manifests suddenly with chills followed by frontal headache, body ache and high temperature, which is continuous and lasts for 5 to 12 days or longer. Cough, pain in the abdomen, diarrhea and vomiting were observed. Bleeding from nose, gums and intestines also reported in severe cases with occasional hemorrhagic manifestations. Neurological abnormalities have also been observed in a few cases; however those were not severe. The virus is highly infectious and many personnel involved in the investigations of the disease fell sick both in the field and laboratory (Banerjee and Bhat, 1984; Banerjee, 1990). In some cases the disease relapsed two to three weeks after the first phase.

Epidemics of KFD have occurred every year since 1957. The number of cases averaged between 400 and 500 per year, with a low incidence in 1961 (less than 40 suspected cases) and highest incidence (more than 1000 cases) in 1976, 1977 and 1983.
No deaths were recorded in 1961, 1964 and 1965; peak mortality occurred in 1983 and 1984, with 150 and 160 deaths, respectively. During KFD epizootics between 1957 and 1975, 2442 monkey deaths have been reported. Thirty-four species of ticks were recorded from KFD area and over a thousand isolates of virus have been obtained from ticks collected in the endemic area. Among all the tick species, *H. spinigera* contributed up to 90% of the isolations and has been incriminated as the chief vector of the virus responsible for epizootics in monkeys and epidemics in man (Work, 1958; Trapido et al., 1959; Verma et al., 1960; Bhat and Sreenivasan, 1981). A total of 528 villages from 5 districts have been recorded as affected from 1957-2004. During 1999 to 2004 the highest numbers of cases were reported in 2003 (Pattnaik, 2006). An increasing trend in the number of cases in the region is alarming and noteworthy.

Investigations by the National Institute of Virology (NIV) conclusively proved that man plays no part in the transmission of the virus in nature. He is only tangentially infected and represents the dead end of the transmission cycle. The disease is seasonal and prevalent between December and the beginning of June with peaks usually occurring between February and May.

A large number of mammals and birds were screened for the presence of the virus and its antibodies and subjected to experiments for determining their susceptibility and viremia levels in order to assess their role in the transmission of the virus (Bhat and Goverdhan, 1973). The study resulted in isolation of the virus from white-tailed rat (*Rattus balfourii*), white-bellied rat (*Rattus rattus wroughtoni*), shrew (*Suncus murinus*) and a bat (*Rhinolophus rouxi*). Neutralizing antibodies were found in cattle, buffaloes, goats, wild boars, porcupines, squirrels, flying squirrels and rats, mice, shrews and a number of species of birds (Anderson, 1970; Anderson and Singh, 1971; Bhat, 1974; Bhat et al., 1978; 1986). Black-napped hare, porcupines, flying squirrels, Malabar giant squirrels, three-striped squirrels, gerbils, mice, long-tailed tree mice and shrews have been shown to circulate high titers of virus. KFD virus has been shown to persist in a latent form in the organs, particularly brain tissues of experimentally infected rodents, such as the spiny mouse, porcupine and long-tailed tree-mouse. KFD virus has also been isolated from bat ticks. Virus neutralizing antibodies have been found in the sera of number of bat species (Pavri and Singh, 1965; 1968; Gadkari et al., 1976; Bhat et al., 1978). Bats might play a role, at least, virus sustenance, in nature and possibly in the transmission of KFDV as depicted by susceptibility studies and virus isolation (Bhat et al., 1979; Bhat and Sreenivasan, 1990). About 2000 birds including red spur fowl and jungle fowl and other
ground dwelling birds have been screened for KFD virus but no isolation has been obtained (Ghosh et al., 1975; Geevarghese and Mishra, 2004). Positive correlation has been found between the intensity of infection in ticks and the total number of human cases of KFD in different areas (Boshell, 1969; Banerjee and Bhat, 1977; Sreenivasan and Rajagopalan, 1983; Bhat, 1985). The epizootic and epidemic activities of the disease have been shown to coincide with the prevalence and activity of the nymphal stages of the tick vectors. Longitudinal studies carried out by NIV have implied that the virus could have been existing in wild conditions in an enzootic form even before 1955. It is concluded that KFD virus circulates in enzootic state through small mammals such as rodents and shrews and ground birds and an array of tick species including *H. spinigera*. When monkeys come in contact with the enzootic cycle, they get infected, amplify and disseminate the infection during epizootics creating hot spots of infection. People who trespass the hot spots get bitten by the infected *H. spinigera*, which is highly anthropophilic and pick up the infection.

The Institute has developed a formalized inactivated chick embryo tissue culture vaccine against KFD. This was the first ever-viral vaccine developed and produced entirely with Indian expertise. This vaccine could evoke the production of neutralizing antibodies in about 59% to 72% of the vaccinated persons (Banerjee et al., 1969; Dandawate et al., 1980). The technology was transferred to the Karnataka Public Health Department, which manufactured over 50,000 doses/year of vaccine in its laboratory at Shimoga and administered the vaccine in the population under risk.

**Origin of the proposal**

Until 1971, KFD was restricted to the contiguous areas of Sagar, Sorab and Shikaripur taluks. However, in 1972, a new focus of virus activity appeared around Gadgeri village in Sirsi taluk, North Kanara district that was followed by emergence of a number of new foci in the districts of Shimoga, North Kanara and South Kanara. Cases keep occurring even today in one or another focus every year during December to May with a case fatality rate of 2 to 10% (Pattnaik, 2006). Though, overt infection is restricted to the KFD area in Karnataka, seropositivity towards KFD virus in man and/or animals has been detected in Gujarat, Rajasthan, Maharashtra, West Bengal, Tamil Nadu and Andaman and Nicobar Islands (Padbidri et al., 2002). So far KFD virus has been detected only in India, however, its closely related species Alkumrah Hemorrhagic virus (AHFV) has been reported in Mecca and Jeddah in Afghanistan, which is thought to be genetic.
subtype of KFDV (Zaki, 1997; Charrel et al., 2001; Charrel and Lamballerie, 2003; 2005; Madani, 2005).

Studies carried out by NIV on various intricate ecological aspects of the disease also infer that anthropurgic conditions caused by human settlements and their recent expansions have a direct bearing mostly on the multiplication and concentration of the vector tick *H. spinigera*. This species feeds on cattle and lives in the interspace between the clearings and primeval forests enclosing the villages. Deforestation has also caused a change in the behavior of monkeys; they are compelled to come down on the ground and come in contact with the high-density tick areas. This has resulted in a latent enzootic infection, circulating mainly through small mammals and ticks, resulting in monkey epizootics and epidemics. These observations suggest that there is need to characterize the KFD strains isolated in India since 1955. With this background the present study was undertaken to look for the characterization of this virus isolated during 4-5 decades.

**Objective:**

Phylogenetic analysis of the available *KFDV* isolated from India (during last five decades), for understanding whether different strains caused epidemics in different areas at different time or they were same.