KYASANUR FOREST DISEASE: A ONE HEALTH REVIEW OF AN EMERGING TICK-BORNE VIRAL INFECTION

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Abstract

Kyasanur Forest disease (KFD) is a zoonotic tick-borne viral haemorrhagic fever endemic to the Western Ghats of India. Since its first recognition in 1957, the disease has expanded beyond Karnataka into neighbouring states, highlighting the influence of ecological change, human encroachment into forest ecosystems, and vector dynamics. KFD virus, a member of the genus Flavivirus, is maintained through a complex transmission cycle involving ticks, small mammals, and non-human primates, while humans act as incidental hosts. This review summarizes the historical development, virology, epidemiology, clinical features, diagnosis, prevention, vaccination, and the importance of a One Health approach for surveillance and control.

Keywords: Emerging tropical disease, Kyasanur Forest Disease, tick borne viral haemorrhagic fever

Introduction

The increasing frequency of zoonotic disease emergence underscores the intricate interdependence between humans, animals, and the environment. Anthropogenic activities such as deforestation, habitat fragmentation, agricultural expansion, and climate change have altered natural ecosystems, facilitating closer interactions between wildlife, domestic animals, arthropod vectors, and human populations. These ecological disturbances have created favorable conditions for the emergence and re-emergence of several vector-borne zoonotic diseases, emphasizing the importance of the One Health approach in disease surveillance and prevention.

Kyasanur Forest disease (KFD), commonly referred to as *monkey fever*, is a tick-borne viral haemorrhagic fever that remains one of India's most significant yet neglected zoonotic infections. First identified in the Kyasanur Forest region of Karnataka, the disease was historically confined to the Western Ghats but has progressively expanded into neighboring states over recent decades (Walsh *et al.*, 2019). The changing distribution of the disease is closely associated with ecological alterations, increasing human activities within forest ecosystems, and the movement of infected vectors and reservoir hosts.

The causative agent, Kyasanur Forest disease virus (KFDV), is a member of the genus *Flavivirus* and is primarily transmitted through the bite of infected *Haemaphysalis spinigera* ticks. Human infection typically occurs following occupational or recreational exposure to forested environments where infected ticks are prevalent. Clinically, KFD is characterized by an acute febrile illness accompanied by severe myalgia, headache, gastrointestinal disturbances, haemorrhagic manifestations, ocular involvement, and, in some patients, neurological complications.

Although supportive care remains the cornerstone of clinical management, no specific antiviral therapy is currently available.

The geographical expansion of KFD beyond its traditional endemic foci highlights the influence of demographic, environmental, socioeconomic, and climatic factors on disease transmission (Chakraborty *et al.*, 2019). Consequently, effective surveillance, timely diagnosis, vector control, public awareness, and sustained vaccination programs are essential for limiting disease spread. This review provides a comprehensive overview of the epidemiology, ecology, pathogenesis, clinical manifestations, diagnosis, prevention, and control of Kyasanur Forest disease while emphasizing the importance of integrated One Health strategies for mitigating its public health impact.

History

In March 1957, high number of deaths were reported among monkeys in the Kyasanur Forest area in the Shimoga District of Karnataka. The locals called it as “Mankan Kayala” (Mourya and Yadav, 2016). This was followed by occurrence of unknown infection in residents nears the forest area. National Institute of Virology, Pune, first isolated the etiological agent from the sick and dead monkeys. Thereafter for seven decades the infection remained endemic to Karnataka only. But with five years, 2012 to 2017,

KFD has expanded to Tamil Nadu, Kerala, Goa and Maharashtra (Munivenkatappa et al., 2018).

Aetiology

This potential zoonotic disease is caused by the KFDV, which belongs to the family Flaviviridae and genus Flavivirus (Chakraborty et al., 2019). It is a positive sense, single stranded, enveloped, RNA virus with an icosahedral nucleocapsid and spherical size (40-65nm). Kyasanur Forest Disease is fatal in humans and non-human primates (John et al., 2014). The virus is highly infectious and is a class 4 biosafety level pathogen.

Vector and reservoir

Haemaphysalis spinigera, is the primary species tick which act as the vector for KFD. Nymphal stage is more infective than adult. The ticks remain infectious throughout their lives (Pattnaik, 2006). Several other genera of ticks have also been shown to be capable of transmitting KFDV, including members of the Argas, Dermacentor, Hyalomma, Ixodes, Ornithodoros and Rhipicephalus.Important reservoir host of KFDV are monkeys, especially two south Indian species, red-faced bonnet macaques (Macaca radiata) black-faced (Hanuman) langurs (Semnopithecus entellus) (Holbrook, 2012). Several species of rodents act as important maintenance host. Especially Blanford's rat, the jungle striped squirrel, common house shrew, field mice, Indian gerbil, frugivorous and insectivorous bats. Cattle also acts as maintenance hosts, but do not amplify the virus (Chakraborty et al., 2019). Man is a dead-end or tangential host of KFDV. There is no report of human-to-human transmission of KFDV (Roy et. al., 2014).

Mode of transmission

The disease has a seasonal occurrence mainly during dry periods (November-June) due to hike in tick population. Most of the epizootics occur during this period. The KFDV is maintained and circulated in small mammals especially rodents, shrews, ground birds and ticks in enzootic areas. Bite of infected ticks spread the infection to wild monkeys. Humans will get infection by the bite from infective ticks while visiting forest areas of endemic areas for recreation, hunting or for collecting wood and herbs. Grazing cattle and birds from endemic area introduce the infection to new areas (John et al., 2014).

Epidemiology

Till 2006, KFD was endemic to five districts of Karnataka State viz. Shimoga, Chikamagalur, Dakshina Kannada, Uttar Kannada and Udupi. But in recent years, its presence has been established in other states across the Western Ghats including Chamarajanagar district in Karnataka, Nilgiri district in Tamil Nadu, Wayanad and Malappuram districts in Kerala, and Pali village in Goa (Murhekar et al., 2015) also from Ker village, Sindhudurg district, Maharashtra (Gurav et al., 2018). Serological evidence of KFDV has been demonstrated from Kutch and Saurashtra in Gujarat state, in parts of West Bengal and has also been found in the Andaman Islands (Roy et al., 2014). Variants of KFDV have also been isolated in Saudi Arabia and China (Holbrook, 2012). During 1995 and 2001, a novel flavivirus was isolated from Alkhumra district, Saudi Arabia, infection from haemorrhagic fever patients hence named as Alkhumra haemorrhagic fever virus (AHFV). Kyasanur Forest Disease Virus and AHFV closely related on genetic level, but are strikingly different in their mode of pathogenesis and tissue tropism (Shah et al., 2018).In May 2013, the first case from Kerala has been documented from Noolpuzha of Wayanad district. During 2014–2015, outbreaks were overtly observed in new regions (Shah et al., 2018). Including three cases from Nilambur, Malappuram district in June 2014, reports of KFDV infection in monkeys from Mannar, Alappuzha District in April 2014.

In 2015, 10 positive cases of KFD have been reported in various parts of Wayanad district - seven cases from the Cheeyambam tribal hamlet in Pulpally gram Panchayat and one each from Padinharethara, Periya and Poothadi grama panchayaths (Muraleedharan, 2016).

Clinical signs

Humans

The incubation period of KFDV varies from 3 to 8 days (Muraleedharan, 2016). The disease has various stages in development. An initial prodromal stage will be followed by haemorrhagic stage and the final long convalescent stage. The initial stage is manifested with sudden onset of fever, chills, headache, gastro intestinal disturbances, insomnia, sore throat, decreased blood pressure and heart rate, pain in muscles and extremities. Haemorrhages in conjunctiva, retina and vitreous humour, keratitis,

opacity of lens, mild iritis are the ophthalmic manifestations of KFD. Low counts of platelet, white blood cells and red blood count will be evident in patients infected with KFDV. Haemorrhagic stage is characterised by irregular epistaxis with blood in vomitus and faeces, blisters on mouth, haemorrhages from the gum and nose (John et al., 2014).A relapse phase of around 2 weeks with same clinical manifestations of first phase along with various neurological complications such as abnormal reflexes, confusion and tremors has been reported (Pattnaik, 2006).

Animals

KFD is an acute fatal disease of animals. Mortality is associated with high viraemic stage. In experimental infections, case fatality rate of around 100%. Macaca radiata might be an excellent model to study disease pathogenesis. The disease manifestation is similar to humans. The animals generally develop peak viraemia between two and five days of inoculation. Within ten days animals will die. Experimental infection with KFDV in bonnet macaques manifested with neurological signs, in second febrile stage (John et al., 2014). Diarrhoea by day 4 after infection was evident.Clinical signs of haemorrhages were not observed (Kenyon et al., 1992). Macaques infected with KFDV show haematological changes such as thrombocytopenia and leucopenia and elevated hepatic enzymes (Bhatia et al., 2020).

Post mortem findings

In humans, nephrosis, hepatomegaly with degenerative changes, pneumonia with haemorrhage in the lung parenchyma, gastro intestinal haemorrhage, distinct reticulo-endothelial cells in liver and spleen, with noticeable phagocytosis of RBC in spleen are the autopsy changes. No pathognomonic lesions are described (Pattnaik, 2006).In monkeys, except from human, cerebral lesions are evident.

Nonpurulent encephalitis with focal microgliosis and perivascular cuffing are the common lesions in brain. Blood clots in anus, haemorrhage in lungs, moderate swelling and pallor of the renal cortex, brain, and adrenals, focal liver necrosis with cytoplasmic inclusion bodies are other findings (Muraleedharan, 2016).

Diagnosis

Virus Isolation

Isolation of the virus utilising BHK–21, Vero E6 cell lines and embryonated chick cell or in mice can be attempted. KFDV will produce characteristic cytopathic effect in BHK–21. Intra–cerebral inoculation of virus in 3-day old mice and intra–peritoneal inoculation in 50-day old mice will cause mortality in all. Due to its high vulnerability to virus, 3-day old Mice are highly recommended for virus isolation (John et al., 2014).

Serological Methods

Haemagglutination Inhibition (HI) test and neutralization test are utilized for demonstration of KFDV antibodies from south western states such as Gujarat and Maharashtra, also from West Bengal and Andaman and Nicobar Islands. IgM capture and IgG ELISA assays were developed using gene sequences of the NS-5/non coding region. These assays can detect KFD viral RNA in acute phase human serum samples. Hence provide early, rapid & accurate diagnosis of infection (Roy et al., 2014). Though, these assays are not yet available in laboratories in endemic areas (Mourya and Yadav, 2016).

Molecular Diagnosis

National Institute of Virology has developed nested RT–PCR and Taq Man-based real time PCR which provides a very rapid and accurate diagnosis. The RT–PCR reactions are highly specific and sensitive compared to other conventional methods, also aids in the rapid detection of KFD during acute phase infection. The primer designed targeting flaviviruses specific NS–5 region (Mourya and Yadav, 2016).

Treatment

Currently, no anti-viral drugs are available to treat KFDV infected patients. Supportive therapy includes maintenance of proper hydration and circulation by transfusion of intravenous fluids, colloids and electrolytes, maintaining oxygen status and blood pressure, and treatment for any medical complications. Patients can be managed using antipyretics, antimicrobial therapy for secondary infections, corticosteroids and anticonvulsants for nervous disorders (Bhatia et al., 2020).

Prevention and Control

Prevention strategies including quarantine, vaccination, early diagnosis and tick control, which will restrict the entry of virus to new areas. Vaccination is the main control strategies for KFD (Kasabi et al., 2013a).

Vaccine

The Indian Council of Medical Research (ICMR) generated the first vaccine against KFDV. It was based on a formalin-inactivated mouse-brain formulation of Russian spring–summer encephalitis virus (RSSEV) due to its genetic and antigenic similarities to KFDV. But the immune responses produced by the RSSEV vaccine were insufficient to prevent KFDV (Bhatia et al., 2020). In 1966, Haffkine Institute in Bombay developed the formalin inactivated virus that was generated in chick embryo fibroblasts, which was licensed and used in India in the endemic areas as routine vaccination since 1991 Chakraborty et al., 2019). The vaccine has two-dose schedule in individuals aged 7-65 years with an interval of two months. This will be followed by booster doses at 6 to 9 months and then every 5 years. Studies specify that, vaccine efficacy is 79.3 per cent with 1 dose and 93.5 per cent with 2 doses (Roy et al., 2014). Though, the vaccine has shown protection under ideal conditions, due to the improper vaccination in endemic areas, it still does not provide a high percentage of immunity against infection. Field evaluation studies also point out the low uptake and insufficient coverage of vaccine (John et al., 2014).

Chemical Control

Benzene hexachloride (BHC) is found to be effective for six weeks. The spraying may be carried out in areas within a radius of 50 meters around the spot of monkey death. Also effective in forest tracks visited by man for various activities (Roy et al., 2014).

Health Education and personal protection

Preventive measures include use of tick repellent (Dimethyl phthalate, NN-Diethyl-mTolumaide), protective clothing's and gum boots to cover the whole body, strictly prohibiting the visit to affected forest areas during outbreak time and initiation and completion of vaccination campaign before November in every year. Health authorities should ensure distribution and proper use of tick repellent by villagers before visiting the forest, especially during spring and summer (Kasabai et al., 2013b).

Conclusion

KFD mainly affect villagers of lower strata residing near the forest area. Reducing the risk of human KFD primarily focuses on reducing the exposure and susceptibility to infection (Burthe et al., 2021). Tick acts s a reservoir host of the infection. Hence it is difficult to eliminate the infection. Evergreen and semi-evergreen forest areas of Western Ghats play a major role in harbouring the infection. Regular vaccination for consecutive five years in endemic area should be carried out to check the transmission of KFD. The concept of 'one world, one health and one medicine' has eminent role while fighting zoonotic infections (John et al., 2014).

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