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REVIEW ARTICLE

KYASANUR FOREST DISEASE: A REGIONAL REPORT OF EPIDEMIOLOGY, PATHOGENESIS, AND ITS CLINICAL MANIFESTATIONS

Tulsi Patel, Parisha Patel, Udit Chaube*

Institute of Pharmacy, Nirma University, Ahmedabad 382481. India.

**uditchoube@gmail.com, ORCID ID: 0000-0002-3130-7510*

ABSTRACT

Kyasanur Forest Disease (KFD), also known as Kyasanur Forest Virus (KFDV) infection, is a virus that mostly affects humans and monkeys. It was first discovered in the Kyasanur Forest in Karnataka, India, in 1957, hence its name is Kyasanur Forest Disease. The Kyasanur Forest Disease virus, a member of the Flaviviridae family and a close relative of the tick-borne encephalitis virus, is the culprit behind KFD. The Haemaphysalis spinigera tick species, which act as the virus's reservoir and vector, is particularly known for carrying the disease through its bite. The primary hosts of KFDV are thought to be monkeys, which also serve as amplification hosts and help the virus propagate among tick populations. Signs and symptoms of KFD are similar to those of other viral illnesses, such as a high fever, headache, muscle soreness, and exhaustion. Some people may experience more serious symptoms, such as hemorrhagic signs and neurological issues which further resulted in death. KFD management mostly involves supportive care to manage symptoms and avoid complications because there is no particular antiviral medication for the disease. The KFD is primarily seen in southern India and is regarded as an emerging infectious disease with a small geographic spread. However, occasional cases and outbreaks have also been documented in nearby areas. In order to provide more efficient prevention measures and therapies for KFD, the present regional report strives to better understand the epidemiology, pathophysiology, and potential risk factors connected with this condition.

Keywords: *Kyasanur Forest Disease, Ticks, flavivirus infection, KFD vaccine*

INTRODUCTION

The Kyasanur Forest Disease (KFD) was initially discovered in a specified forest area in the district of Shimoga, Karnataka. Both the red-faced bonnet monkey (Macaca radiata) and the black-faced langur (Presbytus entellus) had an increase in fatalities in this area in 1957. When people started dying in the surrounding, then it became a concern for the local health department. Since then, 400–500 cases of KFD are thought to have occurred each year in India [1-3]. Due to accounts of a febrile illness in people at the same time, the phrase "monkey disease" became popular [4,5].

For many years, KFD was limited to operating in the Shimoga district and the nearby forests of Uttara, Udupi, and Dakshin Kannada. Recently, the public health department of India has raised concerns about the disease's recent expansion to far-off locations viz. North Kerala, Tamil Nadu, Goa, and a few locations in Maharashtra and Gujarat have all recorded cases of the disease in the last six years [4].

Pathogenesis:

The KFD virus (KFDV), related to the Siberian Alkhurma virus, causes KFD, a flavivirus

(ss RNA virus) infection [4]. This virus is considered to be the most complex virus among all the other types of viruses. Initially, it was considered to be the Russian spring-summer (RSS) virus later on it is named as KFDV virus [6]. Monkeys and Human beings are considered to be the best reservoir of this virus. KFD is a tick-borne viral disorder. The pathogenesis of KFD is shown in Figure 1. When infected with a tick, the condition is maintained throughout life and KFDV can be transmitted to offspring by laying eggs. Cattle serve as hosts to reproduce and spread tick populations but do not participate in the transmission of KFD virus. KFDV spreads by small mammals such as rats, shrews, ground birds, etc. during the enzootic stage [3]. The KFDV usually infects large numbers of monkeys, and very rapidly it replicates itself in the monkey's body. The virus is transmitted to humans by infected ticks. Humans are bitten by tick nymphs (morphological phase of the tick life cycle, usually from November to May in India) when they visit a forest or when they carry nymphs to human dwellings through dried leaves for various uses [4]. The symptoms of KFD are mainly reported to be chills, headache (mainly in the frontal part), muscle pain, vomiting, gastrointestinal problems, bleeding, and heavy fever, with an incubation period of 3-8 days. The overall mortality rate is found to be in the range of 3% to 5% [1].

During the initial outbreak, 466 cases were reported in the state, followed by an additional 181 cases in the subsequent year. By 2003, the KFD had spread to more than 70 villages in four districts bordering Shimoga in the western part of the state of Karnataka.[3]. Early detection can be done by PCR (polymerase chain reaction) or by blood virus isolation. Later, serological testing can be done using an enzyme-dependent immunosorbent serum test (ELISA). KFD is not specially treated as no special treatment is available against this disease. Early hospitalization and supportive care are essential. Supportive care includes the maintenance of hydration and the usual precautions taken for patients with bleeding disorders. Formalin-inactivated indigenous KFD vaccine is available which reduces the incidences of KFD in India however this vaccine needs to be taken for five years as it has many booster doses. Apart from that, even the administration of this vaccine resulted in the recurrence of the disease. Therefore, the Indian Council of Medical Research (ICMR) has taken the initiative for the development of new vaccine candidates against this disease.

Insect repellent and wearing protective clothing in tick-infected areas are the other more preventative measures [7,8].

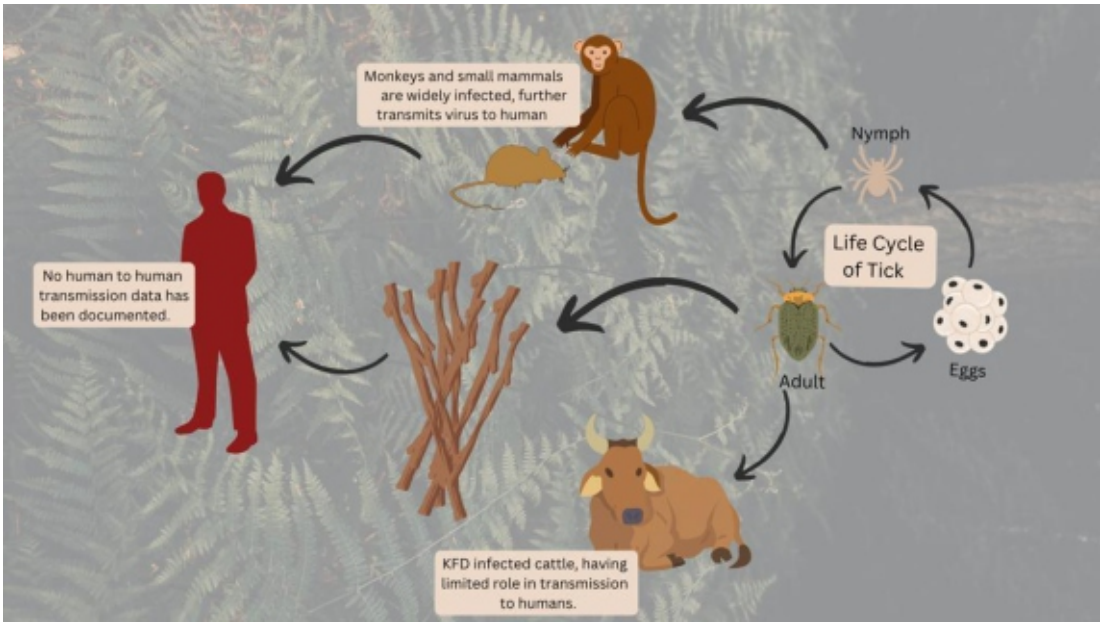

Figure 1: Pathogenesis of Kyasanur Forest Disease (KFD)

Clinical Profile

The monkey illness, also known as Kyasanur forest disease, is mostly found in India's southern region. KFD is included in category A98.2 of the 2017 International Classification of Diseases, 10th edition (ICD-10), under the heading "Other Viral Haemorrhagic Fever" and not elsewhere. Incubation of the KFD lasts 3–8 days in the human body [2-7]. KFD is found to be biphasic, but for now and then it if found that it is majorly divided into four stages. In the first stage, typically, the patient is discovered to have a fever, headache, and broad body aches, particularly in the neck, lower back, and limbs. Conjunctival inflammation is found in sclera and the palpebral is noted during the initial stages. The majority of patients have illness and gastrointestinal symptoms such as nausea, vomiting, and abdominal pain in the early stages of KFD. Fever may get aside but the patient can remain asthenic and lethargic for a longer duration. The patient may also have a lesser fluid intake of the fluid leading to Dehydration. In normal cases, the person may recover from KFD in 10-14 days. But at the time of recovery, the person might suffer from muscle twitching, paraesthesia, and general shivering due to weakness [7].

People not more than 20% suffer from biphasic illness [8]. In this phase, neurological symptoms are the major symptoms that last for 12-14 days. Drowsiness, momentary disorientation, confusion, infrequent convulsions, and loss of consciousness are among the neurological symptoms. The fatality rate is noted to be about 3-5 % which is less than the COVID-19 fatality rate however immediate attention is required for the development of new vaccines and medicines against the KFD [7]. No specific treatment is available for KFD, providing oxygen therapy, maintaining fluid balance, controlling blood pressure and treating further infection are all essential component for supportive care. Several computational techniques are available which can be used for the development of new drugs against this disease [9-11].

Future Perspective

Developments in bioinformatics and computational biology present intriguing paths toward developing potent treatments and vaccines to fight KFD. Using methods like molecular docking, pharmacophore modeling, 3D Quantitative Structure-Activity Relationship (3D-QSAR), and molecular dynamics (MD) simulations can speed up the search for new treatments and greatly improve our understanding of the KFD virus (KFDV).

3-D Quantitative Structure-Activity Relationship (3D-QSAR): The link between the chemical structures of possible antiviral agents and their

biological actions against KFDV can be examined using 3D-QSAR. Key structural elements that contribute to inhibitory activity can be found by researchers by modeling the spatial and electrical properties of these substances[12]. This method makes it easier to optimize lead compounds, increasing their effectiveness and lowering the possibility of negative side effects. Furthermore, 3D-QSAR can help anticipate a new compound's activity prior to synthesis, which helps speed up the drug discovery process.[13-15]

Pharmacophore Modeling: Pharmacophore modeling involves identifying the essential molecular features responsible for the biological activity of antiviral agents targeting KFDV. By constructing a pharmacophore model, researchers can screen large chemical libraries to identify compounds that fit the necessary interaction criteria with viral proteins, such as the viral envelope glycoproteins or non-structural proteins critical for viral replication[13-17]. This method not only streamlines the identification of promising drug candidates but also provides insights into the mechanism of action, guiding the rational design of more potent inhibitors.[12,21]

Molecular Docking: The orientation and binding affinity of possible therapeutic compounds with KFDV target proteins are predicted mostly using molecular docking simulations. Through precise simulation of the interactions between small molecule inhibitors and structural proteins or viral enzymes, docking studies are able to identify which compounds have the best chance of binding and be validated through additional experiments[12-14]. This method is useful for finding inhibitors that can stop vital viral functions like protein synthesis or RNA replication, which prevents viruses from multiplying.[19-24]

Molecular Dynamics (MD) Simulations: MD simulations provide a dynamic perspective on how KFDV proteins interact with possible treatment substances. Molecular Dynamics (MD) simulations of atomic and molecular motions over time shed light on the flexibility and stability of protein-ligand complexes in physiological settings. Understanding how chemicals affect the structural changes of viral proteins and the duration of their inhibitory effects is essential for determining the efficacy of treatment candidates. Additionally, MD is able to locate allosteric sites that could be novel targets for antiviral therapy [21-24].

Integrating these computational techniques into the research pipeline can significantly reduce the time and cost associated with traditional drug discovery methods. Moreover, they enable the exploration of a vast chemical space to identify unconventional or repurposed drugs that may exhibit antiviral properties against KFDV. Collaborative efforts between

computational scientists, virologists, and medicinal chemists are essential to translate these in silico findings into viable clinical solutions.

By finding viral epitopes that generate powerful immune responses, these techniques can help not just with treatment development but also with vaccine creation. By simulating the interactions between various vaccination candidates and the human immune system, predictive models can optimize adjuvant formulation and antigen selection for increased safety and efficacy.

Overall, there is great promise for improving our methods for treating and preventing KFD through the integration of 3D-QSAR, pharmacophore modeling, molecular docking, and molecular dynamics simulations. In order to overcome the obstacles presented by this newly developing infectious disease, it will be essential to keep funding computational research and interdisciplinary collaboration.

CONCLUSION

The Kyasanur Forest Disease (KFD) is mostly seen in southern parts of India. Ticks are the primary vector, and both people and monkeys are susceptible. Symptoms of this disease include mild headaches and fever to more serious neurological problems which might vary from person to person. Tick management is an efficient preventive measure available for the treatment of this disease. There are no antiviral medicines are available against this disease. Recently, the Indian Council of Medical Research (ICMR) asked for the expression of interest from various pharmaceutical industries and academic institutes for the development of a vaccine against KFD. The goal of the present regional report is to better understand and manage this newly developing infectious disease.

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DECLARATION

The Authors declare no conflict of Interest

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None

ETHICAL STATEMENT

The paper is not currently being considered for publication elsewhere. All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

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