Review Article

Kyasanur Forest Disease: An emerging tropical disease in India

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DOI : 10.5455/jrmds.2014221

ABSTRACT

This review article discusses the current problem statement of the Kyasanur forest disease which is mainly neglected but an emerging tropical disease in India. The changing epidemiology and clinical features are described. Geographical clustering with cases has been documented. Newer diagnostic methods have been stated. Along with treatment, preventive aspects, which is the mainstay management has been discussed in details.

Key words: Kyasanur Forest Disease, emerging tropical disease, tick-borne.

INTRODUCTION

Arbovirus (arthropod borne virus) have been recognized in recent years as a significant public health problem, with the emergence and re-emergence of various arboviral diseases world-wide, particularly in Southeast Asia [1]. Outbreak of arboviral diseases such as dengue, Japanese encephalitis and Chikungunya fever have been recognised as a public health problem and have been included under the National Vector Borne Disease Control Programme in India [2]. On the other hand, Kyasanur forest disease (KFD) remains largely a neglected and unaddressed disease despite reports of recent outbreaks [3].

PROBLEM STATEMENT

Studies indicate that KFDV may be persisting silently in several regions of India. Despite extensive vaccination efforts, from January 1999 through January 2003, an increasing number of KFD cases have been detected in Karnataka. Since the identification of KFD in 1957, there has been an estimated of 400–500 cases per year in India. In India, from 2003 to 2012 there were 3263 suspected cases, with 823 confirmed cases and 28 deaths, a case fatality rate of 3.4% [4]. Though the number of cases had declined from 2005 to 2010, there has been a resurgence of the disease in December 2011 to March 2012 with around 314 cases. Cases started reporting this year among residents of Shimoga district of Karnataka where out of 20 suspected cases, 12 samples were tested and 6 were confirmed positive by RT-PCR by first week of February 2014.

EPIDEMIOLOGY

Agent & Vector factors: KFD, also known as monkey fever is a tick-borne disease caused by a highly pathogenic virus called KFD virus (KFDV). Initial serologic studies revealed that KFDV is related to the Russian spring-summer encephalitis complex of arboviruses, now renamed as the tick-borne encephalitis (TBE) sero-complex of flaviviruses [5]. It is a member of the family Flaviviridae, genus Flavivirus. It is an Arbovirus belonging to Casal's group B. KFDV is zoonotic. Various tick species, mainly *Haemaphysalisspinigera*, act as vectors for KFDV. In addition to many different tick species, it involves a number of small and large mammals and probably birds in its natural cycle which upon tick bite becomes reservoir for this virus. KFDV commonly targets two monkey species—black-faced Langurs (Semnopithecus entellus earlier classified *Presbytis entellus*) and red-faced bonnet monkeys (Macacaradiata). They become infected with KFDV through the bite of infected ticks. When infected monkeys die, ticks spread from the body that further cause dissemination of the virus [6,7,8]. Intensive investigations over the years have implicated several species rodents as important maintenance host. Man is a dead –end or tangential host and of no significance in the natural history of the KFDV. There is no evidence of person to person transmission of KFDV.

KFD is limited to six districts (Chamarajanagar, Chikkamagalore, Dakshina Kannada, Shimoga, Udupi and Uttara Kannada) of Karnataka State, India, where each year during January–May, 100–500 persons are affected by the disease [9]. KFDV or related viruses have been demonstrated to be present in other parts of India, including parts of Kutch and Saurashtra in Gujarat state, and in parts of West Bengal [10]. Serological evidence of KFDV has also been found in the Andaman Islands [11]. Detection of KFDV in Bandipur National Park of Chamarajanagara District in Karnataka, Mudumalai forest in Nilgiri district of Tamil Nadu and Noolpuzha in Wayanad district of Kerala 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.

Variants of agent - Omsk Hemorrhagic fever virus, which is endemic in western Siberia, Russia is distantly related to KFDV. Alkhumra virus was first isolated in Saudi Arabia as a causative of hemorrhagic fever and is genetically a close relative of KFDV [12, 13]. The gene sequence of a Nanjianyin virus isolated in a febrile patient in Yunnan, China was found homologous to that of KFDV [14]. The genotyping studies conducted on 48 KFD viruses isolated over the past five decades in India showed a low level of diversity with a maximum of 1.2% and 0.5% a differences seen among these viruses [5]. Results of molecular epidemiologic studies have suggested that tick-borne flaviviruses have evolved slowly while dispersing north and west across Asian and European forests [15, 16, 17]

Host factors: why humans are at risk to get the disease? With rapid, uncontrolled deforestation and along with increased human activities in forest area without protective measure, there is significant increase in chance of transmission of the disease to humans

CLINICAL FEATURES & DIAGNOSIS

As per International Classification of Disease-10, KFD has been classified under A98.2. KFD has an incubation period of 3-8 days. As per studies, KFD passes through various stages. i.e. a prodromal stage lasting 12 days or longer characterized by high grade fever with chills, frontal headache, myalgia, photophobia, severe prostration, hypotension and hepatomegaly. This stage is followed by a stage of complication characterized by haemorrhage including epistaxis, haemoptysis, and gastrointestinal bleeding including melena. Relapse of the symptoms are often observed after 1 to 2 weeks of the first febrile period, last for 2 to12 days. KFD may be biphasic in presentation. The relapse phase displays same symptoms as the first phase and in addition neurological symptoms such as altered sensorium and reflex abnormality are often seen. Pulmonary haemorrhage and massive gastrointestinal haemorrhage are terminal complications that can cause death [18, 19].The convalescent phase is generally prolonged, maybe up to 4 weeks. KFD patients in convalescence can be lethargic for weeks and often results in tremors due to weakness of muscles but it eventually resolves. Long-term sequels are uncommon.

Examination of blood shows leucopaenia, thrombocytopenia and decreased haematocrit during early phase followed by leucocytosis after 3 weeks. Albuminuria appears in most cases. CSF is clear in most cases except in second phases with meningeal signs, where an increase in cells and protein is noticed.

The diagnosis is made by virus isolation from blood or by serologic testing using enzyme-linked immunosorbent serologic assay (ELISA). Recent developments include a nested RT-PCR and a Taq Man-based real time RT-PCR and IgM anti-bodies capture ELISA. These assays were developed using gene sequences of the NS-5/non coding region and detected KFD viral RNA in acute phase human serum samples and can provide early, rapid & accurate diagnosis of infection.

TREATMENT

There is no specific treatment except supportive and symptomatic ones. Analgesics, maintenance of hydration and nutrition along with rest are the mainstay of treatment. Blood transfusion is done if the situation demands. No particular measures of isolation of patients seem to be indicated.

PREVENTION

Vaccine: The first KFD vaccine was a formalin-inactivated, mouse-brain preparation of Russian Spring Summer Encephalitis Virus (RSSEV) produced by Indian Council of Medical Research due to the close antigenic resemblance of KFDV with RSSEV. But studies found that the RSSEV vaccine did not stimulate a strong immune response against KFDV, nor did it prevent KFD [20]. Subsequent efforts were redirected

towards production of a vaccine based on KFDV, rather than RSSEV. A formalin-inactivated chick embryo vaccine was developed in the Haffkine Institute in Bombay [21] licensed and used in India. It is given in a two-dose schedule to individuals aged 7-65 years with an interval of two months, followed by booster doses at 6 to 9 months and then every 5 yearly [22]. Studies indicate a vaccine efficacy of 79.3% with 1 dose and 93.5% with 2 doses [23]. Under the Directorate of Health and Family Welfare, Karnataka, vaccination campaigns using formalin inactivated tissue culture vaccine have been implemented in districts where KFD is endemic. Villages reporting KFD activity (laboratory-confirmed cases in monkeys and/or humans, or infected ticks), and all villages within 5 km of the affected location are targeted for vaccination. If cases of KFD are reported in the area in spite of vaccination during the pre-transmission season, additional vaccination campaigns are conducted.

Chemical Control: Source reduction is also an important control measure against ticks. – Benzenehexachloride (BHC) as wettable powder has been found to be effective for six weeks. The spraying may be carried out in areas where monkey deaths have been reported (within a radius of 50 meters around the spot of monkey death). It is also effective in forest tracks frequented by man for various forest activities.

Health Education and personal protection: In the affected areas, humans visit the forest area for their livelihood, and get infected through tick bites. Use of tick repellent (Dimethyl phthalate, NN-Diethyl-m-Tolumaide) should be advised to the local villagers, forest camp workers and staff, tourist and wild-life photographers. People should also be educated to wear long-sleeved clothes that reduce exposure to ticks.

Legislative measure: Control, policy formation & strict administrative measures against increased rate of illegal felling of trees and deforestation need to be ensured.

FUTURE PERSPECTIVES

Internationally, KFDV is ranked as one of the highest risk categories of pathogens belonging to Bio Safety Level-4 and has thus serious biosafety concern. The current distribution of KFD is limited to relatively restricted areas of India, Saudi Arabia and China [24]. This distribution of KFDV spanning across such widely separated areas in India, China and Saudi Arabia suggest the possibility that KFDV has a wide mobility. Also the possibility that KFDV does exist in other areas of the world in cryptic enzootic cycles cannot be ruled out. We might thus be sitting with a ticking time bomb with the very real threat of KFD epidemics breaking out in hitherto virgin areas. The danger may be further augmented by the pressure of ever expanding population on the limited natural resources leading to hazardous ecologic changes such as intrusion into forest by humans and large scale deforestation with associated tick displacement. Further, 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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Date of Submission: 01/04/2014
Date of Acceptance: 24/05/2014

How to cite this article: Roy P, Maiti D, Goel MK, Rasania SK. Kyasanur Forest Disease: An emerging tropical disease in India. J Res Med Den Sci 2014;2(2):1-4.

Source of Support: None
Conflict of Interest: None declared