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A REVIEW ARTICLE ON CHIKUNGUNYA VIRUS

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ABSTRACT

The recent emergence of Chikungunya has taken the concern of the health authorities of Bangladesh. There was a good number of record of Chikungunya patients in different hospitals as well as clinic. Although the fatality rate of this disease almost negligible, but the suffering due to this viral fever has been the main notable point. The aim of this paper is to make a general understanding of the disease as well as the structural identity of the virus with the symptoms and probable treatment or prevention.

KEYWORDS: Chikungunya, Bangladesh, Emergence, Health, Mosquitoes.

INTRODUCTION

In 1955, Chikungunya was first officially described from an outbreak in Tanzania, Africa, 1952. In 2007, there was an outbreak in Italy which causes significant concern in Europe. From October, 2006, SriLanka experienced the incidence of Chikungunya. In 2008, Chikungunya was first identified in Bangladesh. An outbreak of undiagnosed pain and fever was reported in Dohar, Dhaka District in late October, 2011.[1] According to Institute of Epidemiology, Disease Control and Research Officials, on average, about 7-10 cases of chikungunya were found in a week of May, 2017.[13]

Chikungunya virus genome organization

In 1953 Chikungunya virus (CHIKV) was first isolated from Tanzania. Based on the E1 gene sequence of the virus by phylogenetic analysis, it is classified into three genotypes- Asian (A), East/Central and South African (ECSA) and West African (WA). These genotypes are

responsible to cause the epidemics in their respective areas, except for ECSA genotype. ECSA genotype has also been found to be present in Asia in recent years (Singh and Unni, 2011). CHIKV is a member of Alphavirus genus. The virion is only 70 nm in diameter whereas genome size is 11.8 Kb and is an enveloped positive strand RNA virus that has icosahedral symmetry.[2, 4, 6]

There are 240 heterodimers of transmembrane glycoprotein (E1 and E2) that repeat one after another and form trimeric spikes on its surface. 80 trimeric spikes have been found to be present on the surface of a mature virion. Again, some small peptides, E3 and 6K are also present in the structure. The function of E3 is to interact with E2 glycoprotein and form spikes as well as to direct structural proteins to the endoplasmic reticulum that ensures their proper assembly.[7] On the other hand, 6K is involved in the assembly and budding process of the virus[11] and in alphaviruses it also forms a cation selective ion channel.[12] There are also 2 open reading frames (ORFs), that are located in the 5′ end and 3′ end. The ORF in the 5′ end encodes non structural proteins (nsP1-nsP4) while the ORF in the 3′ end encodes structural proteins with amino acid poly chain. There is also an un-translated junction that separates the two ORFs.[2,4] It has been reported that this junction is responsible for containing the internal promoter for the transcription of the sub-genomic mRNA in sindbis virus (alphavirus).[14] In virus replication the function of the nonstructural proteins are different from one another. For the initiation of viral RNA synthesis and RNA capping nsP1 is responsible, while nsP2 is important for protease and RNA helicase activities. The formation and localization of replication complexes involve three domains of nsP3. RNA-dependent-RNA polymerase (RdRp) activity is mediated by nsP4 that is crucial for the replication and synthesis of viral genome.[15]

Replication

Chikungunya virus replication is not fully elucidated in terms of molecular mechanism in mammalian cells. But the replication cycle is similar to other alphavirus replication cycles. The virus target host cell by endocytosis (receptor mediated) that involves clathrin coated vesicles[3]**.** DC-SIGN, L-SIGN, heparin, lamina, integrin and sulphate are some receptors that are involved in the entry processes of alphaviruses. In case of CHIKV a new receptor protein prohibitin have been identified.[5] Once the virus enters the target cell, the acidic endosomal environment plays a role for the conformational change of the virus envelop. As a consequence, CHIKV membrane is fused with host endosomal membrane due to the

exposure of E1 glycoprotein. In this process the core viral genome is released into the cytoplasm.[7] The viral mRNA translates precursors of nonstructural proteins that get cleaved into nsP1-nsP4. Viral replication complex is formed when these proteins assemble. This replication complex synthesizes a full length negative sense RNA intermediate that act as a template for downstream synthesis of both genomic (49S) and subgenomic (26S) RNAs.[4] The Capsid-pE2-6K-E1 polyproteins are derived from the translation of 26S subgenomic mRNA. Serine protease further processes them and in the cytoplasm the capsid is released. Post translational modification of the remaining proteins occurs when they reach the endoplasmic reticulum. When the Golgi is cleaved by pE2 then glycoproteins (E2 and E3) are generated. These glycoproteins will then be heterodimerize and form trimeric spikes onto the virion surface after reaching the plasma membrane of the host cell. 49S genomic RNA containing icosahedral nucleocapsid is produced by the assembly of capsid protein. Mature virions obtain a membrane bilayer from the plasma membrane of host cell and they assemble at plasma membrane and start the budding process.[7, 17] The replication of chikungunya occurs between 8 to 16 hours after infection[7] and in mammals the virions are produced at 37° C in less than 8 hours after infection.[3]

Transmission

There are two distinct transmission cycles involved in chikungunya- the urban cycle and the sylvatic cycle. The urban cycle involves man-mosquito-man and the sylvatic cycle involves animal-mosquito-man. The sylvatic cycle is common in Africa and is maintained between wild primates and *Aedes* species of mosquitoes of the forest. Among them Aedes furcifer, *Aedes luteocephalus, Aedes taylori* and *Aedes africanus* are common. In Asia the urban cycle predominates. In case of the urban cycle the human body serves as hosts and the Aedes species of mosquitoes serve as vectors. *Aedes aegypti* is the major vector for the transmission of CHIKV as it is well adopted in the urban areas. But in recent years Aedes albopictus is also reported to cause epidemics. Both the species can coexist with humans in the rural as well as urban areas and have the ability to breed in comparatively clean water of artificial drink containers or other materials.[2,18]

Pathogenesis

Female mosquito bites predominate in the transmission of chikungunya virus.[19] Infected mosquitoes bite the host and infects through inoculation at the skin. Infection is spread through fibroblasts and dermal macrophages.[3,8] Virus replication initiates host immune

response.[9,7] The virus via circulatory system rapidly disseminates into lymph nodes.[9] In the peripheral tissue virus replication occurs and the virus can be transmitted via mosquito biting.[10] When the virus reaches target organs (muscle, joints, the liver and the brain) immune response is generated.[19]

Immunological Responses to Infection

After infected mosquito bite the skin serve as the portal entry of the virus to the body and initially it affects resident cells like keratinocytes, melanocytes, dendritic cells and contribute to spread virus to other target organs.[20]

Chikungunya infection is a cytopathic event that can rapidly cause cell apoptosis as a result of innate immune response. Apoptotic blebs that are released from dying cells increase the chance of infection as the infection is spread to neighboring uninfected cells. Again macrophages worsen the situation by inducing phagocytosis of infected cells and releasing CHIKV containing blebs to circulation and interfere with host immune response. Another cellular process involved in CHIKV infection is autophagy in which the replication process of CHIKV is increased dramatically in humans.[22]

Innate immune response

It is the first line defense mechanism of the body. Monocytes, NK cells are some blood leukocytes that provide innate immunity to various viral infections. These cells accelerate virus dissemination as their main location is in peripheral tissue and circulatory system. In case of CHIKV infection both hematopoietic and nonhematopoietic cells are involved by the innate immune system.[23]

Type I IFN provides antiviral pathway and plays a crucial role against viral infection. IFN-α and IFN-β plays a viral antiviral role in case of CHIKV infection.[3] Increased level of the production of IL-6 can cause persistent arthralgia as the virus infects cells of knee-joints.[7] The increased level of NK cells also contribute to joint inflammation.[24] Again, monocytes/macrophages in the circulatory system can disseminate virus infection as well as it can also serve as a reservoir for further viral infection.[23]

Adaptive immune response

Chikungunya infection can give protection through adaptive immunity. It has been observed that if anti-CHIKV immune response is once established then it can completely protect host

from reinfection by CHIKV.[20] The role of T cells in infected patients have not been fully elucidated but it was observed that in the early stages of the disease CD8+ T cells play significant role while CD4+ T cells dominate in later stages of the disease to give humoral response.[7] Again anti-CHIKV antibodies are another possible strategy to target CHIKV infection.[21]

Symptoms

Symptoms of a patient usually begin after he or she has been bitten by an infected mosquito. Symptoms include headache, muscle pain, joint swelling, rash, fever and joint pain. Among these, fever and joint pain are the most common symptoms of chikungunya. Though the result of this disease is not death, the symptoms may persist for months or even more. These may be severe and disabling. Newborns who are infected around the time of birth, adults aged ≥65 years and people with high blood pressure, diabetes or heart disease are more susceptible or at higher risk for more severe disease. It is said that if a person is infected once, he or she will likely to be protected from further infections in future.[16]

Treatment

No vaccine or medicine is discovered yet to prevent or to treat chikungunya virus. There are some recommendations to treat the symptoms of chikungunya fever which includes:

a. Plenty of rest should be taken
b. Prevention of dehydration by drinking fluids
c. Administration of acetaminophen or paracetamol to reduce pain and fever
d. Aspirin and other non-steroidal anti-inflammatory (NSAIDs) should be avoided
e. Consultation with physician before taking other medications for another medical conditions
f. Prevention of mosquito bites is recommended for the first week of chikungunya attack. This is mandatory as the virus can be transmitted during the first week after attack.[16]

CONCLUSION

There is a proverb, ‘Prevention is better than cure’. This is highly significant in case of chikungunya attack. The outbreak of chikungunya is now a matter of concern. There is treatment available though the vaccine or specific medicine has not discovered yet. The treatment pattern is related to dengue, but unlike dengue, the pain is severe. As the carrier of this virus is mosquito, the avoidance of mosquito bite is the main preventive measure to prevent chikungunya fever.

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