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Review Article

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ZIKA VIRUS ANOTHER EMERGING ARBOVIRUS – A REVIEW

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ABSRACT

The aim of this review article is to focus on the risk factors of Zika virus and threat to public health.Zika virus is mosquito borne Flavivirus related to Yellow fever virus, Dengue virus, Japanese encephalitis virus, Chikungunya, West nile virus. Zika virus is the genus of Flavivirus in the family Flaviviridae and the group is- Group IV ((+)ssRNA. It is considered an emerging arbovirus transmitted by Ades mosquitoes which usually bite during the morning and late afternoon or evening hours. The principle vectors that spreads Zika virus are Aedes aegypti and Aedes albopictus which are the native to Africa and Asia. The symptoms of illness are Acute fever, Maculopapular rash, Arthralgia, Headache, Conjunctivitis, Severe neurological complications like Guillain-Barre syndrome an autoimmune syndrome frequently culminating in limb paralysis and Zika virus in pregnant women might cause congenital abnormalities like microcephaly.

KEYWORDS: Arbovirus, ZIKV, Flavivirus, Aedes, Microcephaly, Flaviviridae.

INTRODUCTION

Zika virus (ZIKV) is mosquito borne Flavivirus (Aedes) related to Yellow fever virus, Dengue virus, Japanese encephalitis virus, Chikungunya, West nile virus. Zika virus is the genus of Flavivirus in the family Flaviviridae and the group is- Group IV ((+)ssRNA). The first confirmed case of Zika virus was reported in 1947 in a monkey in Zika forest of Uganda (Africa) which gave it the name Zika.[1] It is closely related to the dengue virus. Zika virus—an arbovirus found in Africa and Asia-Pacific and transmitted via *Aedes* mosquitoes (Figure- 1).

Figure 1. Female Aedes aegypti mosquito.

Vector mediated transmission of ZIKV is initiated when a blood feeding female Aedes mosquito injects the virus into the skin of its mammalian host, followed by infection of permissive cells via specific receptors. Indeed, skin immune cells, including dermal fibroblasts, epidermal keratinocytes, and immature dendritic cells, were all found to be permissive to ZIKV infection. "Arbovirus" is a descriptive term applied to hundreds of predominantly RNA viruses that are transmitted by arthropods, notably mosquitoes and ticks. Arboviruses are often maintained incomplex cycles involving vertebrates such as mammals or birds and blood-feeding vectors. Until recently, only a few arboviruses had caused clinically significant human diseases, including mosquito- borne alphaviruses (Zika virus is a member of the *Alphavirus* genus in the family *Togaviridae*) such as chikungunya and flaviviruses such as dengue and West Nile. The most historically important of these is yellow fever virus, the first recognized viral cause of deadly epidemic hemorrhagic fever. Aedes aegypti mosquitoes commonly found in tropical and subtropical regions around the world. These viruses started to emerge millennia ago, when North African villagers began to store water in their dwellings. Arboreal *A. aegypti* then adapted to deposit their eggs in domestic water-containing vessels and to feed on humans, which led to adaptation of arboreal viruses to infect humans.[2] Aedes albopictus also transmits the Zika virus. Zika virus disease is caused by an RNA virus transmitted to humans by Aedes mosquitoes, especially by the Aedes aegypti species.[3] Around 80% of Zika virus infected persons are asymptomatic. The symptomatic disease generally has low grade fever, skin rashes, arthralgia (notably of small

joints of hands and feet, with possible swollen joints), myalgia, asthenia and conjunctivitis.[4]

HISTORY OF ZIKA VIRUS

Zika virus is a mosquito borne Flavivirus that was first isolated from a rhesus monkey in the zika forest (Zika meaning is overgrown in the lugandan language) of Uganda in April 1947.[5] Scientists were able to isolate a new transmissible agent from the sick monkey (caged rhesus monkey (macaca mulatta)), which was named Zika virus, or ZIKV. Antibodies against Zika virus were first identified in humans in the early 1950s. The first confirmed case was reported in the year of 1952 in Nigeria. Less number of cases where reported in Africa and Asia until 2007. In 2007, however, a major epidemic occurred in Yap Island, Federated States of Micronesia. The first major outbreak, with 185 confirmed cases, was reported in 2007 in the Yap Islands. More recently, epidemics have occurred in Polynesia, Easter Island, the Cook Islands and New Caledonia. A recent larger outbreak of Zika virus outside Africa and Asia was confirmed in April 2015, in Brazil. Brazilian health authorities reported more than 3,500 microcephaly cases between October 2015 and January 2016.[6,7] Zika virus has been blamed for a 20-fold rise in cases of microcephaly among neonates in Brazil.[7] The country is currently experiencing the largest epidemic ever recorded with 440,000 to 1,300,000 suspected cases reported by the Brazilian health authorities. Zika virus and it's serological (virus identification in blood) presence have been identified in Africa and Asia – and most recently, in countries across Latin America.[8] The increased frequency of Guillain-Barré syndrome and congenital neurological anomalies notified by the Brazil Ministry of Health.[9] Its first detection in Uganda but ZIKV has appeared in the following countries of Africa and Asia: Gabon, Egypt, Nigeria, Senegal, Sierra Leone, Côte d'Ivoire, Central African Republic, Cambodia, Micronesia, Malaysia, Pakistan, India, Thailand, Philippines, and Indonesia.[10]

ABOUT THE VIRUS

ZIKV is an envelope, icosahedral, arbovirus of the family *Flaviviridae*, genus *Flavivirus* (figure- 2); it is phylogenetically and antigenically related to the *Spondweni virus.*[11] Zika virions are typically icosahedral-shaped with a non-segmented, single-stranded, positive sense RNA genome. They are enveloped, 18-45 nanometer in diameter. Zika virus is a single-stranded RNA virus with a genome length of 10,794 nucleotides encoding 3,419 amino acids. The genome encodes a polypeptide that produces three structural and seven nonstructural proteins; the structural proteins include the capsid, envelope, and membrane complex. The Zika virus genome encodes for two polyproteins – the non structural polyprotein consisting of four proteins (nsP1, nsP2, nsP3 and nsP4) and the structural polyprotein consisting of five proteins (Capsid, E3, E2, 6K and E1) (Figure- 3). The 5' end of the RNA molecule is capped with a 7-methylguanosine while the 3' end is poly-adenylated. A subgenomic positive-strand RNA referred to as 26SRNA is transcribed from a negative-stranded RNA intermediate. This RNA serves as the mRNA for the synthesis of the viral structural proteins. *Alphaviruses* have conserved domains that play an important role in the regulation of viral RNA synthesis. These domains are found at the 5' and 3' ends as well as at the intergenic region. The E1 and E2 glycoproteins are expected to form heterodimers that associate as trimeric spikes on the viral surface covering the surface evenly. The envelope glycoproteins play a role in attachment to cells. The viral envelope protein interacts with several cell surface receptors and attachment factors, whose differential expression determines the cellular tropism of the virus. The entry receptors and the factors such as heat shock proteins, laminin receptor, integrin αvβ3, prohibitin, claudin-1, scavenger receptor class B, and natural killer cell receptor NKp44, can interact with viral particles in mammalian and/or mosquito cells, but their exact role in the flavivirus entry program, as well as their physiologic relevance, is not well understood.[12] Virions located on the surface of the cell membrane enter the host cells by fusion and endocytosis of the viral envelope. The virion is approximately 40 nm in diameter with surface projections that measure roughly 5–10 nm. Nucleocapsid is 25-30 nm in diameter surrounded by a host-membrane derived lipid bilayer. The uncoating of the virions occurs in the cytoplasm. The site of mRNA transcription is in the cell cytoplasm. Replication is not restricted to a particular tissue or organ of the host so the virus replication occurs in various organs. The insect host initiates the virus replication.[13] The genome replication is done in the cytoplasm. Nucleotide sequence analyses have identified two major Zika virus lineages, an African and an Asian lineage, each of which contains multiple strains of virus. Strains belonging to the Asian lineage have been disseminated geographically and have become indigenous in distant regions, including parts of the Americas.

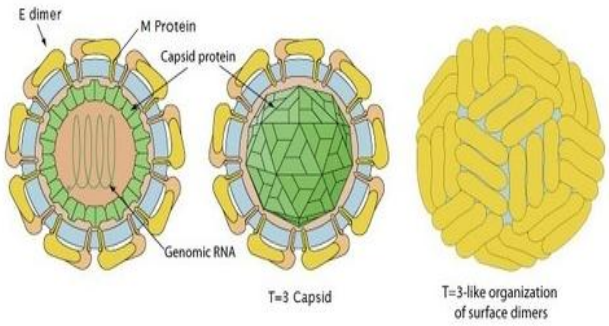

Figure- 2. Structure of Zika Virus

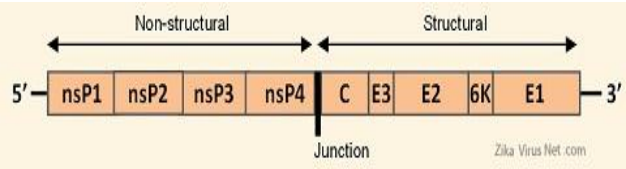

Figure- 3. Zika virus genome structure

CLINICAL MANIFESTATION

ZIKV disease is around 80% is asymptomatic. Infection with the Zika virus may cause acute illness that clinically resembles dengue fever. ZIKV infection (symptomatic) is usually characterized by Mild Fever, Arthralgia (small joints of hands and feet), Myalgia, Headache, Asthenia, Abdominal pain, Edema, Lymphadenopathy, Retro-orbital pain, Conjunctivitis, and Cutaneous Maculopapular rash, Sore throat, Rhinorhea.[14, 15, 16] The incubation period is typically 3–12 days. There is no specific therapy for Zika virus infection and acute symptoms typically resolve within 4-7 days.

TRANSMISSION

Zika virus is transmitted to people through the bite of an infected mosquito from the *Aedes* genus, mainly *Aedes aegypti* in tropical regions. The mosquito usually bites during the morning and late afternoon/evening hours. The same is the source of transmission of dengue, chikungunya and yellow fever. Recent case shows that human-to-human contact is possible, which would make it the first time an insect-borne disease was passed via sexual contact.[17]

ZIKA VIRUS AND PREGNANCY

Pregnant women become infected with Zika virus which transmits the disease to their unborn babies. Reports from several countries like especially Brazil, there is a concurrent increase in severe congenital abnormalities such as Microcephaly and Guillian-Barre syndrome.[18] Zika virus infections have been confirmed in infants with Microcephaly, and in the current outbreak in Brazil, a marked increase in the number of infants born with microcephaly has been reported.[19] All pregnant women consider postponing travel to areas where Zika virus transmission is ongoing. Zika virus may be connected to the autoimmune disorder Guillain Barré, which causes "ascending motor paralysis" and "interferes with the ability of nerves to function and survive".[20] Most of the baby's were affected with Microcephaly in Brazil and a brief idea about the Microcephaly.

Microcephaly

Microcephaly is a clinical finding, defined as a head circumference more than 2 SDs (two standard deviation) below the mean for age and gender that may result from any insult disturbing early brain growth. Head circumference that falls below the -3 SD is sometimes referred to as severe Microcephaly. The occipitofrontal head circumference should be determined by placing a measuring tape around the cranial vault to include the widest part of the forehead and the most prominent part of the occipital area to arrive at the largest possible measurement. If abnormal, at least a second measurement should be performed to confirm the result. Microcephaly is a condition where a baby's head is much smaller than expected (Figure- 4). The small head is the result of a neurodevelopmental disorder. During pregnancy, a baby's head grows because the baby's brain grows. Microcephaly can occur because a baby's brain has not developed properly during pregnancy or has stopped growing after birth, which results in a smaller head size. Microcephaly can diagnose by using ultrasound during pregnancy. CT scan or MRI can provide the information of the baby's brain structure or growth which is helpful to determine the newborn had an infection during pregnancy.[21] Microcephaly can present at birth and can be termed "primary" Microcephaly as opposed to "secondary" Microcephaly, which develops later. Indeed the term primary Microcephaly should be used to imply genetic influences, whereas secondary Microcephaly would designate factors that are environmental in nature (infectious like rubella cytomegalovirus or toxoplasmosis, vascular, traumatic).[22] Other problems linked with Microcephaly are seizures, developmental delay, and intellectual disability, problems with movements, hearing loss and vision problems. These problems are mild to severe; sometimes life threatening.[23] Microcephaly is a lifelong condition and there is no known cure or standard treatment for Microcephaly.

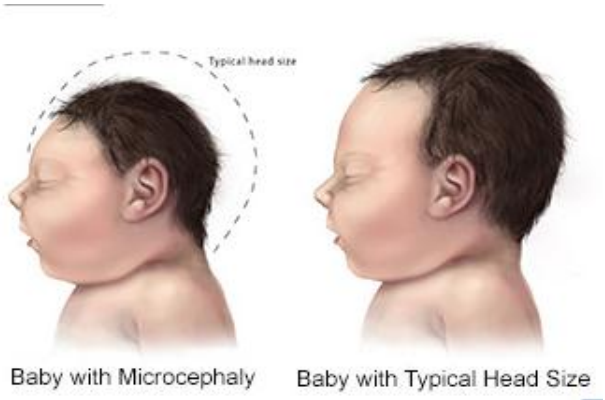

Figure- 4. Baby with Microcephaly and normal head size

TREATMENT

No specific antiviral treatment is available for Zika virus infection. Prevention is the best means for which to control infection and spread of the virus. Treatment is generally supportive and can get plenty of rest, Drink enough fluids to avoid dehydration, and use of analgesics and antipyretics. Fever and pain should be treated with acetaminophen. Do not take aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen and naproxen. Aspirin and NSAIDs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage (bleeding). If a person is on medication for another medical condition, a healthcare providers assistance is needed before taking additional medication.[19, 24] If symptoms worsen, they should seek medical care and advice. Deaths are rare.

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