ZIKA VIRUS- A REVIEW

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ABSTRACT- Viroids and prions might have existed early at the border of inanimate and living worlds. Viruses can only replicate within another living cell, using its "machinery" The Zika virus (ZIKV) is a newly emerged pathogen in the Western hemisphere. Zika virus (ZIKV) is a mosquito-transmitted flavivirus that has emerged as a global health threat because of its potential to generate explosive epidemics and ability to cause congenital disease in the context of infection during pregnancy. ZIKV infection symptoms range from asymptomatic to Gullain–Barré syndrome and extensive neuropathology in infected fetuses. The rapid development of cell culture and animal models has facilitated a new appreciation of ZIKV biology. This Review focuses on details history, important updates and gaps in the knowledge of Zika virus.

Keywords: Zika Virus, Microcephaly, Aedes Mosquito, ZIKV vaccines

INTRODUCTION

Zika virus is enveloped, and has segmented, single stranded, 10 kilobase positive sense RNA genome. It is most related to Spondweni virus and is one of the known viruses in the Spondweni virus clade. Virus particles are 40 nm in diameter with an outer envelope and a dense inner core. Zika virus belongs to flavi-virus genus.

Zika virus is a mosquito borne illness that is spread by the Aedes mosquito, the same species that transmits the dengue and chikungunya viruses. Unlike malaria carrying mosquitoes, Aedes is most active during day. Zika virus(ZIKV) is a member of virus family Flaviviridae. It is spread by day time active Aedes mosquitoes. Its name comes from the Zika forest of Uganda where the virus was first isolated in 1947. ZIKV is related to dengue, yellow fever, Japanese encephalitis and West Nile viruses. Since the 1950 it have been known to occur within narrow equatorial belt from Africa to Asia. From 2007 to 2016 the virus spread, across the Pacific Ocean to Americas, leading to 2015-16 ZIKV epidemics.

HISTORY OR BACKROUND

Zika virus was first found in 1947 in forest of Uganda, Africa in rhesus monkeys[1]. Zika virus was later detected in humans in 1948 for first time in Nigeria. There were approximately 14 to 15 cases recorded until 2007. In 2007 first zika outburst in was documented in Micronesia[2]. Other Pacific islands have had periodic outburst since then. In May, 2015 PAHO (Pan American Health Organization) issued an alert with

respect to Zika virus infections in Brazil[3]. WHO has recorded around 23 countries and territories in Americas from where local transmission of Zika virus has been recorded [4].

Maximum numbers of cases have been recorded till date from Brazil, Venezuela, Honduras, and Colombia. The current epidemic has affected around 1.3 million people in the world with majority of them in Brazil country. There have been 35 cases of travel-acquired Zika infections recorded from USA. On 1ST February, 2016 WHO announced Zika virus disease to be a PHEIC (Public Health Emergency of International Concern.

In 5th February Epidemiological update of European Centre for Disease control and prevention, 36 countries or territories have recorded cases of Zika virus infection in past 9 months. In Brazil, the most affected country, the recent data regarding according to Ministry of Health weekly epidemiological update on monitoring of microcephaly published on 2ndFebruary, 4,783 cases of microcephaly have been recorded since week 43-2015, of which 1,132 were investigated. Of these 36% have confirmed microcephaly[5].

PATHOGENESIS

Zika virus is a virus of flavi-virus category of arbovirus type. These are RNA viruses which are enveloped viruses and are transmitted by arthropod bites. Zika virus falls into same category of virus as of virus causing Dengue, Chikungunya, Yellow fever and West Nile Fever[6]. ZIKV has a single stranded non-segmented positive sense RNA genome. Arthropods i.e. vectors feed themselves on viremic hosts. Zika virus is primarily transmitted by bites of Aedes aegypti mosquito from infected person to others. Zika virus can also be transmitted from pregnant women to fetus intrapartum and during time of delivery.

Aedes aegypti is a vector of this virus which has a wide presence throughout the world. Thus Zika virus disease has potential for international spread given wide geographical distribution of vector. Hence countries like India need to be vigilant. The incubation period of Zika virus has been reported Around 7 to 10 days. Primarily, host of virus are monkeys and humans.

The pathogenesis of virus is hypothesized to start with infection to dendritic cells followed by a spread of lymph nodes and bloodstream. These viruses have been found in infected cell nuclei. The most dangerous time is thought to be during first trimester of pregnancy when some women do not realize that they are pregnant[7].Researchers still don't know how virus enters into placenta and damages the growing brain of fetus.

VIRAL LIFE CYCLE

Even though life cycle of Zika virus is still unclear, according to research life cycle of Zika virus is relate to sylvatic transmission cycle. It is classified as an arbovirus i.e. transmitted through one vertebrate to another by mosquito bite. The virions exist as immature, mature (infectious) and fusogenic states. Humans are incidental hosts in the life cycle of the virions. Monkeys and apes can also serve as host to virions, while some studies have found that elephants, sheep and goats had antibodies against ZIKV suggesting possible host states as well[21].

The cycle starts when an Aedes mosquito ingests blood containing ZIKV after biting an infected person. The ZIKV starts replicating in the epithelial cells of midgut and goes to salivary glands of the mosquito vector. After incubation period after 10 days, the saliva becomes infected making mosquito as a vector for

infecting a human being. Upon entry into human skin the virus infects dermal fibroblasts that serve as receptors for attachment of ZIKV [22]. Up regulation of TLR3 m RNA expression is triggered and this leads to enhanced innate immune response. Interferon alpha and beta are produced by infected cells to help lower viral load. ZIKV can also lead to the autophagy of host cells and inhibitors to this step can be a potential treatment option in future, once replication is complete the virus spreads to regional lymph nodes hematogenously, infecting organs such as nervous system. Moreover in pregnancy conditions virus can go through placental blood barrier to infect the fetus.

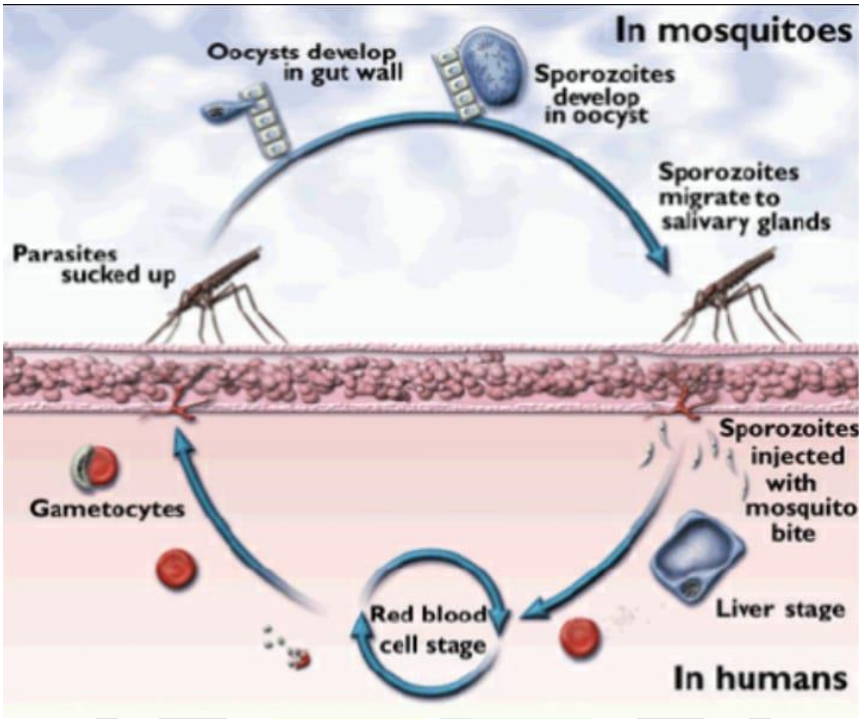

Figure: Life cycle of Zika Virus

TRANSMISSION

Zika virus is commonly transmitted by mosquito bite, primarily of Aedes (Stegomyia) genus [11]. These Aedes have been implicated, including Ae. Aegypti, Ae. Africanus, Ae. Hensilli and Ae. Albopictus [12]. They are active in day and late morning and evening. These mosquitoes are carrier of virus once they have drawn blood from individual who has been infected with Zika virus, once infected mosquitoes are able to spread virus to others. These mosquitoes have un-noticeable bite and have ability to bite multiple humans in single meal. When a female Ae. Aegypti bites to human, she injects virus through her saliva, and virus is present in her salivary glands. Additional modes of transmission have been identified including:-

- Mother-fetal transmission by transplacental process and during delivery by infected mother to fetus.
- Sexual transmission has been also possible from asymptomatic male to women through body fluids as late as 5-6 weeks after onset of the man's symptoms. Viral RNA can be found in vaginal fluids, semen and urine.
- Blood transfusion and organ transplantation from infected donor also pose a potential risk of transmission [13].

- Infection can also occur in the laboratory during occupational activities.

Recent studies are concidering the chances of Zika virus infected mother transmitting the virus to infants by breastfeeding. Some studies suggest that the Zika virus can identified in breast milk of infected mothers, although there is not sufficient data of confidently conclude that Zika virus can transmitted by this manner.

MAJOR POSSIBLE SYMPTOMS

The common symptoms of Zika virus are quite broad in nature and are characteristic of many flavi-viruses such as Dengue and Chikungunya [8]. When symptoms occur, they are non-specific, self-limiting similarly to other arbovirus infections.

The symptoms can persist for 3-12 days and include myalgia, fatigue, arthritis, edema, fever, headache, retro-orbital pain, and conjunctivitis, maculopapular rash on face and limbs, vomiting and other digestive disorders [8, 9]. Less commonly reported symptoms are lymphadenopathy, prostatitis, anorexia, vertigo and hematospermia [10]. Before the outburst in French Polynesia in 2013 there were neither severe presentations of these symptoms nor hospitalization.

GENERAL LABORATORY FINDINGS

Information on laboratory findings for ZIKV infection is limited. Complete blood count is often normal even if blood count is abnormal i.e. changes may be non-specific (eg. Mild neutropenia, mild lymphopenia, moderate thrombocytopenia). Mild elevations in inflammatory markers (fibrinogen and ferritin), serum lactate, and dehydrogenase or liver enzymes have been described [23]. These findings are observed in many viral infections including DENV and CHIKV so none of these laboratory alterations reliably distinguish among these infections.

Laboratory Diagnosis

- Plaque reduction neutralization test (PRN) for the determination of virus specific neutralizing antibodies is the standard for differentiation of anti-Flavi-virus antibodies.

- Zika virus infection can also be diagnosed with rapid tests.

- This infection can be diagnosed in clinical samples by serology using immunoglobulin M to detect specific antibodies against the ZIKV enzyme immunoassay antigen by nucleic acid amplification methods such as acute phase sera using immune fluorescence assay.

- ZIKV infection can be diagnosed in the blood, urine, sperm/semen and in saliva.

- Infection can be diagnosed in cerebrospinal fluid, amniotic fluid, and other tissues [16].

DIAGNOSIS

There are mainly two tests for detection of ZIKV which are as follows:-

PCR test: - It is useful in first 3 to 5 days after onset of symptoms. It helps in direct detection of ZIKV virus RNA or specific viral antigens in clinical specimens.

Serology test: - It detects the presence of antibodies within 5 days after onset of symptoms [27]

Clinical detection is unreliable for a diagnosis of ZIKV infection. Because of clinical overlap with other viruses diagnosis relies on laboratory testing. Evaluation for ZIKV, CHIKV and DENV should be undertaken concurrently for all patients who have rashes, acute fever after recent travel to an area of ongoing ZIKV transmission. Commercial assays have been developed including a PCR based assays [28]. Testing has been performed by large references universities and laboratories. Suitable tests are selected by laboratories on basis of clinical data providing by requesting healthcare provider to coordinate sample collection, providers should contact local public health agencies before testing. Serum samples remain the most specific diagnostic approach and are preferred testing method for ZIKV during acute phase of illness [29]. In contrast, serologic testing is not recommended during acute phase at that time ZIKV IgM may be undetectable. However, testing should be performed during viremic period.

The type of sample can affect the probability of identification. Although diagnostic testing is performed primarily on CSF or serum, the diagnostic utility of other specimen types is being evaluated. Saliva and urine may use as alternatives; specifically blood collection is difficult [30]. One study reported that ZIKV RNA is detected in urine up to 20 days after viremia had become undetectable. So, RT-PCR testing of urine should be considered when ZIKV is clinically suspected, despite negative serum testing. The clinicians should keep a high degree of suspicion of ZIKV infection in those people who present with its symptoms and have history of travel in areas which have reported to be affected with ZIKV in last two weeks.

COMPLICATIONS

In adults the main complications of ZIKV are neurological, including meningitis, myelitis and meningoencephalitis. Severe complications of this disease are decreased auditory acuity; transient, monotonous or metallic hearing; delay between sound emission and perception and Guillain Barre Syndrome.

Zika virus infection may impair some functions of placenta, contributing fetal growth restriction and placental insufficiency. During pregnancy the ZIKV may cause ZIKV-associated neurological syndrome; cerebral intracranial calcifications, ventriculomegaly, neural cell death , congenital neural malformations, brain stem dysfunction, ocular abnormalities, auditory dysfunctions, pigmentation and loss of foveal reflex, macular atrophy, sensorineural hearing loss, choriorentinitis, ophthalmological and auditory changes[14,15].

Children affected by Zika virus during pregnancy may exhibit ophthalmologic, auditory, articular, urogenital, convulsions, irritability, dysphagia, hydrocephalus, diffuse astrocytic, cerebellar dysgenesis, abnormal corpus callosum development, irregular grooves, polymicrogyria, lissencephaly, neuron migration abnormalities, cortical, motor and mental retardation, osteoarticular abnormalities[16,17,18].

New born baby can have short head, congenital bilateral feet, craniofacial malformations, hypertelorism, flat face, low nasal bridge and short nose and craniosynostosis due to ZIKV infection.

There are reports of abortions during 1st and 2nd trimester of maternal infections as well as death of adults, pregnant women and newborns.

Link with congenital birth defects:-

Brazil and French Polynesia have reported many cases of congenital brain and spine malformation, specifically microcephaly [19]. Infants born with microcephaly have a smaller and un-developed brain which leads to developmental retardation and can be deadly sometimes.

In 2015, Brazil has reported 1,761 cases of microcephaly. A baby born with microcephaly tested positive for ZIKV has died after few days [20]. This discovery has taken stream of media attention on ZIKV virus outburst in Brazil. Also health care professionals have confirmed an increase in disorders of CNS with spreading of ZIKV and most commonly is the neuro-degenerative Guillain-Barre syndrome (GBS). WHO and other Health Organizations have advised people to study Zika virus infection symptoms and people in pandemic areas specifically pregnant mothers, to take precaution against mosquito bites.

TREATMENT

Still there is no specific antiviral drug for Zika virus infection [9, 24]. The treatment of ZIKV infection is supportive to rest, abundant fluid intake, adequate nutrition. The treatment of ZIKV is totally based on symptomatic relief- a combination of anti-histamines for rashes, antipyretics such as acetaminophen for pain and fever, and fluids for rehydration are prescribed [9, 24, 25]. It has been noticed that infection can be complicated by administering acetylsalicyclic acid which increases the risk of bleeding [26]. To avoid the risk bleeding, one should avoid aspirin and anti-inflammatory drugs. The risk of hemorrhaging is thought to be increased by use of non-steroidal anti-inflammatory drugs (NSAIDS). This is based on the observation of hemorrhagic syndrome onset with other flavi-viruses brought upon by treatment with NSAIDS[25].

MANAGEMENT AND PRECAUTION

No specific treatment or vaccine is available for ZIKV infection. General measures focus on prevention of mosquito bites including individual protection like use of long pants, light colored clothing, bed nets, etc. Community level strategies targets mosquito breeding through elimination of potential egg laying sites by using insecticide treatment. Especially, children and elder people should be taken more precaution [31, 32].

Pregnant women residing in countries that are not ZIKV endemic should not travel to affected countries. Testing should be offered to all pregnant women who have traveled to areas with ongoing ZIKV transmission [33]. Serial fetal ultrasounds should be considered to examine fetal anatomy and growth every 3-4 weeks in pregnant women with positive Zika virus results, and the infant should be tested at the time of birth. Men who reside in or have traveled to an area of active Zika virus transmission and who have pregnant should abstain from sex throughout the pregnancy or use condoms during sex; similar guidelines apply for men with a non-pregnant partner who is concerned about sexual transmission of ZIKV [34]. People returning from affected areas should adopt safer sexual practices or abstain from sex for at least 6to 8 weeks after their returning even if they don't show any symptoms [35].

Information dissemination to the public by different methods like billboards at airports, educating healthcare professionals, hospitals to create awareness about Zika virus. Surveillance at various stages is very important to prevent the spread of this outburst and also to control the infection. Thus physicians and other healthcare professionals should be sensitized towards monitoring cases. The healthcare providers should keep a high degree of suspicion and elicit histories of travel and report accordingly. An international and national collaboration at various levels is equally important to prevent the control of this outburst.

VACCINES ON ZIKV

Recently there has been lot of research ZIKV vaccines, but unfortunately hardly any have made it to market. Only effective DNA vaccines would be favored more over vaccines made out of live or weakened the virus. The need and racing clinical trials shows a necessity to develop vaccine quickly. The best clinical trial models used were rhesus macaques, mice and human [36].

Mouse model: - Clinicians conducted experiments in mice and reported 6 ZIKV antibodies out of which 4 neutralize Asian, African and American strains of mosquito transmitted virus [37]. Inactivated virus vaccine or plasmid DNA vaccine provides safety in mice against Zika virus in single immunization.

Rhesus macaques: - Researchers supported by NIAID also tested the inactivated ZIKV vaccine in sixteen rhesus macaques. They were given two injections for four weeks. After challenged with ZIKV the animal doesn't show detectable virus. In next experiment, the researchers administered two doses of an experimental DNA vaccine, one dose of an adeno-virus vector vaccine to 3 groups of 4 monkeys each. Monkeys were then exposed to ZIKV for 4 weeks [38].

CASE STUDY

In Canada there have been a few reported cases of travelers returning with ZIKV infection. The first case of infection in Canada was in 2013, when a lady who had travelled to Thailand returned to her native place in Alberta, Canada. She experienced a number of mosquito bites during her journey. Upon her return and over a seven day period, the patient experienced intermittent periods of chills and fever, rashes, back pain on her extremities, mild conjunctivitis, joint and muscle tenderness as well as retro-orbital headache[39]. Then she sought out medical attention and it was initially noticed that she had contracted Dengue fever. From the patient, Fonseca and colleagues report that blood; nasopharyngeal swab and urine samples were collected and proceed to differential diagnosis of causative pathogens.

The patient was detected to be negative for bacterial pathogens and malaria, but the blood samples resulted in a positive reaction to IgM antibodies for Dengue virus. An inconsistency was discovered with diagnosis of Dengue fever when patient's serum samples did not show a corroborating positive report to Dengue IgG antibodies [40]. This encouraged the medical staff treating her to look at alternative flavi-viruses. RT-PCR was performed on patient's serum, urine, and nasopharyngeal samples. The complete Zika viral RNA genome was isolated from the urine samples and nasopharyngeal swabs at National Microbiology Laboratory in Winnipeg, Manitoba, Canada. It was confirmed that patient was first host of ZIKV in Canada, having contracted the Zika virus infection from vector from her visit to Thailand [41].

CONCLUSION

Zika virus disease is caused by a virus transmitted primarily by Aedes mosquitoes, which bite during the day.

Symptoms are generally mild and include fever, rash, conjunctivitis, muscle and joint pain, malaise or headache. Symptoms typically last for 2–7 days. Most people with Zika virus infection do not develop symptoms.

Zika virus infection during pregnancy can cause infants to be born with microcephaly and other congenital malformations, known as congenital Zika syndrome. Infection with Zika virus is also associated with other complications of pregnancy including preterm birth and miscarriage.

An increased risk of neurologic complications is associated with Zika virus infection in adults and children, including Guillain-Barré syndrome, neuropathy and myelitis. No specific treatment or vaccine is available for ZIKV infection. General measures focus on prevention of mosquito bites including individual protection like use of long pants, light colored clothing, bed nets, etc.

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