

Evolution and Current Scenario of Zika Virus Infection: A Review

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ABSTRACT

Zika virus is a mosquito borne Flavivirus (genus), which belongs to the family Flaviviridae, a member of arbovirus. This genus includes several viruses such as Yellow fever virus, Japanese encephalitis virus, Dengue virus and West Nile virus. In 1947, Zika virus was first isolated in Zika forest, near the Lake Victoria in Uganda from a febrile sentinel Rhesus monkey. In 1948, it was also isolated from a pool of *Aedes africanus* mosquitoes during a Yellow fever study. In 1952, the virus was first investigated and isolated from humans in East Africa and Uganda respectively. Zika virus was active in several countries in Africa and Asia before spreading to Pacific regions and America. In between 2007-2013, sporadic cases were reported in travelers (Thailand, Cambodia and Indonesia). From April 2007-August 2007, the health care authorities reported 185 cases of Zika virus infection, including 108 confirmed cases on the Island of Yap belongs to the Federal states of Micronesia, in Pacific Ocean. According to WHO, 3 cases were reported in Ahmadabad in India. Currently, the infection is treated only for symptomatic relief such as: Fever is generally managed with damp clothes, light clothing, baths or showers (physical cooling measures). If fever persists paracetamol is recommended. For itchy rash antihistamines like chlorpheniramine is recommended. In case of pregnancy (1st trimester) loratadine and cetirizine (H₁ antagonists) are usually advised because they do not show any adverse fetal outcome during pregnancy especially regarding teratogenicity. Recently, sofosbuvir an antiviral is clinically approved for treating Zika infection. Other broad spectrum antivirals like ribavirin, interferons and favipiravir are not usually prescribed as they show toxic effects in pregnant women. Novobiocin previously an antibiotic is now used as a potent anti Zika drug. As it is a rare infection which lacks availability of drugs and vaccines due to limited research. To combat complication of Zika virus infection symptomatic treatment is recommended. For implementation of the effective vaccine further research is needed to prevent the morbidity and complications.

Keywords: Zika virus, Flavivirus, *Aedes africanus* mosquitoes

INTRODUCTION

Zika virus is a mosquito borne Flavivirus (genus), which belongs to the family Flaviviridae, a member of arbovirus. This genus includes several viruses such as Yellow fever virus, Japanese encephalitis virus, Dengue virus and West Nile virus. In 1947, Zika virus was first isolated in Zika forest, near the Lake Victoria in Uganda from a febrile sentinel Rhesus monkey [1]. In 1948, it was also isolated from a pool of *Aedes africanus* mosquitoes during a Yellow fever study [2]. In 1952, the virus was first investigated and isolated from humans in East Africa and Uganda respectively. It has shown positive association with serum containing neutralizing antibody. From 1964-1970, about 15 types of arboviruses were isolated from humans in Nigeria. Between 1977-78, in Malaysia and Indonesia, huge strains of Zika virus were detected, when *Aedes aegypti* upsurged. Potential increase of Zika virus infection is majorly seen at the end of rainy season. In 1999, during the investigations of Yellow fever virus, 3 strains of Zika virus were isolated in the Ivory Coast [1]. Zika infection was not confined to Asia and Africa, but also the migration of infection was noticed in Yap islands (Micronesia) in the year 2007 [3]. Large outbreak of infection was seen in French Polynesia, New Caledonia, Cook Islands and Easter Island in 2013 and 2014. In 2015, microcephaly, which is a congenital disorder, caused by Zika virus was first reported in Brazil and by the end of the 2015 about 3000 babies were born with microcephaly [4]. Zika virus infection was also detected among people in Nigeria, Uganda, Egypt, India, Pakistan, North Vietnam, Thailand, Malaysia, Indonesia and Philippines and also in North and West of Wallace line.

EPIDEMIOLOGY

After first evidence of human infection in 1952, Zika virus was active in several countries in Africa and Asia [5] prior to the spread in Pacific regions and America. 38% of individuals in Nigeria (1971-1975), had neutralizing antibodies to Zika in their sera [6]. In Indonesia, this infection was serologically confirmed in 3.1% of febrile patients [7]. Since 2007, between 0.5 to 1.5 million cases of Zika have been observed, where Zika virus has continued its East ward direction, which was detected in French Polynesia (2012-2014), Easter Islands (2014) and Brazil (2015) [8]. Since 2015, 49 countries and territories have experienced their first report of Zika virus out break which were previously Zika negative. Zika virus transmission has been documented in 66 countries and territories [9]. In between 2007-2013, sporadic cases were reported in travelers (Thailand, Cambodia and Indonesia) [10]. From April 2007-August 2007, the health care authorities reported 185 cases of Zika virus infection, including 108 confirmed cases in the Island of Yap belongs to the Federal states of Micronesia, in Pacific Ocean [11]. From the beginning of the epidemic to February 2014 in French Polynesia (FP), at an estimation of 29,000 population (10% of population), 8510 cases were reported [12]. Brazil has experienced an unsurpassed epidemic of Zika virus with approximately 30,000 cases [12]. Concomitant epidemic of 73 cases of Gullian Barre syndrome and other neurological conditions were documented in FP in a population of approximately 270,000 [13]. Microcephaly was first investigated in Brazil in 2015 and by mid February 2016 more than 4300 cases has been recorded (due to over reporting and misdiagnosing, it has rose to this number) [14]. In US, 5359 symptomatic Zika virus disease cases reported (508 cases in travelers returning from affected areas, 224 cases acquired through presumed local mosquito borne transmission, 48 acquired through other routes including sexual transmission) and in US territories 36,598 symptomatic Zika virus cases reported (144 cases in travelers returning from affecting area, 36,454 cases acquired through presumed local mosquito borne transmission) [15].

INDIAN EPIDEMICS

According to WHO, 3 cases were reported in Ahmadabad in India. According to WHO statement, the BJ Medical College in Ahmadabad was investigated a case of Zika virus by RT-PCR test and 2 additional cases were detected through the acute febrile illness and antenatal clinic. Around 93 blood samples were collected in between 10th-16th February at BJ Medical College, where they detected a positive for Zika in 64 years male patient. Indian Council of Medial Research (ICMR) has tested 34,233 human samples 12,647 mosquito samples for the presence of Zika virus. Among those, close to 500 mosquito samples were collected from Bapunagar area, Ahmadabad district in Gujarat, and were found negative for Zika [16].

PATHOPHYSIOLOGY

Viral molecular pathogenesis

Zika virus is an icosahedral enveloped single standard positive sense RNA virus with approximately 11,000 nucleotides, which contains multiple copies of complex capsid protein [17]. A single polyprotein containing 3423 amino acids is encoded to viral genome. By several viral and cellular proteases, the polyprotein is processed into three structural proteins, i.e., capsid, membrane and enveloped proteins. These structural proteins are primarily responsible for formation of virus particles and has pivotal role in virus attachment, entry and encapsulation. It addition, it also involves in formation of seven non-structural (NS) proteins-NS₁, NS₂A, NS₂B, NS₃, NS₄A, NS₄B and NS₅ which mediates viral genome replication polyprotein processing and counteraction of host innate antiviral response. Of all these NS protein NS₁ has prominent role in viral replication. Zika virus has a 3 non coding region with conserved sequences organized in a CS₁-CS₂-CS₃ pattern. This is new for the Spondweni virus group. Kedougou and Bagaza viruses have also been sequenced with Genbank accession numbers AY632540 and AY632545 respectively. Based on the partial sequence of NS₅ protein, Bagaza virus is 98% identical to Israel Turkey virus (ITV) Genbank EU303198, both viruses show a high degree of immune (neutralization similarity) [18]. For rapid detection and identification of Flavivirus was developed using a set of universal oligonucleotide primers through a reverse transcriptase (RT-PCR) protocol. Among the mosquito borne Flaviviruses the highly conserved virus corresponds to sequences in the 3-non coding region and in the NS₅ gene. A less numbers of nucleotide were investigated from the C-terminus of NS₅ gene (i.e., about 291-297 nucleotides showed 56-76 similarities when compared to the 3-non coding region which is having more number of nucleotides (i.e., 193-42 nucleotides) showed only 26-36% similarity. Nucleic acid hybridization test was used to detect the recombinant plasmids containing the Flavivirus sequences, from the RT-PCR products derived

from the virus RNA which were extracted from experimental mosquitoes [19]. In 2010 the virus was isolated through gel purification technique in Cambodia. It is then subjected to PCR; it has produced a 100 bp fragment with 100% sequence identity to GenBank accession number EU545988 to Zika virus with nucleic acid position 8,969 of NS₅ gene by Haem agglutination-inhibition tests [20].

Pathogenic mechanism of Zika virus

When a female Aedes mosquito, sucks the blood of an infected patient. Then Zika virus replicates in the mosquito mid gut epithelial cells and later in the salivary gland cells, for the transmission. After the incubation period (5-10 days) virus can be found in mosquito's saliva which subsequently infect humans [21]. For viral maintenance, they may also undergo vertical transmission [22]. Zika virus transmits to vertebrates through the skin puncture, where it passes through the epidermal, dermal and Langerhans's cells of skin. Virus possibly targets fibroblasts, epidermal keratinocytes and immature dendritic cells [23]. It also migrates to the lymph nodes (regional), to the blood stream and at last to the tissues and organs including CNS, skeletal muscle and myocardium. In case of vertical transmission proliferation and hyperplasia of Hofbauer cells (placental macrophages) [24] occurs. Type-1 interferones, pro-inflammatory cytokines and antiviral gene expression are induced by the viral replication that leads to the disruption of feotoplacental barrier. This subsequently leads to microcephaly [25] (caused due to reduced neuron generation and results in small brain with or without cortical gyration anomalies) [26].

TRANSMISSION

Zika virus is transmitted by mosquitoes, primarily by "Aedes" genus like *Aedes africanus*, *Aedes aegypti*, *Aedes hensilli*, *Aedes albopictus* [27]. Non vector borne transmission includes sexual transmission, transmission via placenta/breast milk, saliva or droplets, urine, conjunctival/lacrimal fluids [28]. Whereas sexual, trans-placental transmission and associated neurological morbidities, i.e., Guillianbarre syndrome and microcephaly are unique features of Zika infection. It is also transmitted through infected blood and organ donation.

CLINICAL MANIFESTATIONS

Clinical manifestations are majorly characterized by rashes-77% (mostly maculo papular rashes on patient abdomen arms and legs), myalgia-77%, arthragia-73%, fever-73% and other minor symptoms include edema of extremities, headache, retro orbital pain, periarticular swelling, vertigo, digestive disorders, no purulent conjunctivitis, asthenia, chills, leucopenia, submandibular or cervical lymphadenopathy.

DIAGNOSIS

Generally the infection was diagnosed based on symptoms and history (travel to or from the Zika suspected areas). And majorly it is confirmed by analyzing the laboratory parameters, which includes nucleic acid testing (for onset of symptoms \leq 7days), serology (IgM detection for onset of symptoms \geq 7 days) and also PCR, hem agglutination inhibition test by collecting the samples of body fluids such as blood, saliva, urine and semen [29].

TREATMENT

Currently, the infection is treated only for symptomatic relief such as: Fever is generally managed with damp clothes, light clothing, baths or showers (physical cooling measures). If fever persists paracetamol is recommended. For itchy rash antihistamines like chlorpheniramine is recommended. In case of pregnancy (1st trimester) loratadine and citrizine (H₁ antagonists) are usually advised because they do not show any adverse fetal outcome during pregnancy especially regarding teratogenicity [30]. Recently, sofosbuvir an antiviral is clinically approved for treating Zika infection [31]. Other broad spectrum antivirals like ribavarin, interferons and favipiravir are not usually prescribed as they show toxic effects in pregnant women [32]. Novobiocin previously an antibiotic is now used as a potent anti Zika drug [33].

DISCUSSION

Zika virus is most commonly caused by mosquito bites (mostly by Aedes species) and rarely it can also transmit via body fluids like saliva, urine, semen. Through trans-placental transmission it leads to microcephaly (congenital abnormality). Fever, maculopapular rashes, arthralgia, and myalgia are prominent manifestations of Zika. As these symptoms are similar to dengue and chickenguniya differential diagnosis is mandatory to confirm the infection. As

the commercial tests for Zika virus infection are limited in number, availability and the guidelines for laboratory test, the diagnosis remains suboptimal. Particularly the diagnosis is offered to all the pregnant women who have travelled to the Zika suspected areas to prevent complications associated with Zika virus. Various aspects related to pathogenesis of Zika virus were left unclear. However Zika associated neurological mechanisms were actively investigated. Microcephaly (congenital abnormality) first reported in Brazil in 2015. By the end of 2016 many cases related to microcephaly were reported. The new cases of Zika virus infection should be monitored for complications, particularly babies born with microcephaly. For symptomatic relief Antipyretics and Analgesics are recommended. As there is no specific treatment or vaccine available for Zika virus infection, supportive measures like rest and intravenous infusions are recommended. Currently preventive measures are primary choice, which includes avoiding overcrowding, maintaining hygiene, usage of mosquito repellants and air conditioning.

In mid-2016, WHO in collaboration with UNICEF and a working group of independent subject matter experts developed a Zika virus vaccine target product profile (TPP) for use in an emergency or in a future outbreak scenario. This TPP was revised in February 2017 taking into consideration new data that emerged since the original document was published. On June 1-2, 2017, the WHO convened a group of about 30 experts in epidemiology, regulatory, preclinical and clinical vaccine trials, and mathematical modelling, in a workshop on planning for Zika vaccine efficacy trials.

CONCLUSION

As it is a rare infection which lacks availability of drugs and vaccines due to limited research. To combat complication of Zika virus infection symptomatic treatment is recommended. For implementation of the effective vaccine further research is needed to prevent the morbidity and complications.

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