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Zika virus an emergent mosquito borne infection: Review of literature.

N.S Neki[*], Neeraj Joshi[**], Gaurav Joshi[***], Gagandeep Singh [****], Khushpreet Singh [**], Gagandeep Singh Shergill[**], Rubal Sharma[*****]

[*]Professor, [**]Junior Resident Department Of Internal Medicine, Government Medical College & Guru Nanak Dev Hospital, Amritsar, Punjab, India, 143001.
**** Research Associate, Department of Neurology, University Hospitals Cleveland Medical center, Cleveland, Ohio (USA)
*****Intern Department of Internal Medicine, Government Medical College & Guru Nanak Dev Hospital, Amritsar
*** Assistant professor Pharmacy Department, DDM Group of Institutes Una, Himachal Pradesh, India
Corresponding author: **Dr. N.S. Neki,** Professor of Internal Medicine, Govt. Medical College and Guru Nanak Dev Hospital, Amritsar, India
E-mail: *drneki123@gmail.com*

Abstract

Zika virus is a mosquito borne flavivirus that is an emerging pandemic and public health emergency. Previously limited to sporadic cases in Africa and Asia, the emergence of Zika virus in Brazil in 2015 heralded rapid spread throughout the Americas. "The Ministry of Health and Family Welfare, Government of India (MoHFW) reported three laboratory-confirmed cases of Zika virus disease in Bapunagar area, Ahmedabad District, Gujarat State, India," the global health body said in a statement. India has strengthened its surveillance system in the past few years to detect and contain new infections. Only three Zika cases have been detected in around 50,000 tested so far, a senior Health Ministry official said.

Keywords: Zika virus, *Flaviviridae*, symptoms, diagnosis.

Introduction

The virus was first isolated in April 1947 from a rhesus macaque monkey that had been placed in a cage in the Zika Forest of Uganda, near Lake Victoria, by the scientists of the Yellow Fever Research Institute, later identified in *Aedes africanus* mosquitoes from the same forest.[1]

First evidence of human infection, 1952

Zika was first known to infect humans from the results of a serological survey in Uganda, published in 1952.[2]

Spread in equatorial Africa and to Asia, 1951–1983

Serological studies in several Africa and Asian countries indicated the virus had been widespread within human populations in these regions.[3] The first true case of human infection was identified by Simpson in 1964,[4] who was himself infected while isolating the virus from mosquitoes. From then until 2007, there were only 13 further confirmed human cases of Zika infection from Africa and Southeast Asia.

Present trend of spread

Historically, symptomatic Zika virus infections were limited to sporadic cases or small clusters of patients .This pattern changed in 2007, when the first major outbreak of Zika virus infection occurred in Yap (Federated States of Micronesia), where ≈73% of the population were infected and symptomatic disease developed in ≈18% of infected persons [5]. Since then, Zika virus infection has spread rapidly. Outbreaks have occurred in French Polynesia , Cook Islands, Easter Island , New Caledonia , and, most recently, the Americas [6], with sporadic exportations to Europe.

As of early 2016, a widespread outbreak of Zika was ongoing, primarily in the Americas. The outbreak began in April 2015 in Brazil, and has spread to other countries in South America, Central America, North America, and the Caribbean. In January 2016, the WHO said the virus was likely to spread throughout most of the Americas by the end of the year;[7]

Cases in India

AHMEDABAD: India's first three cases of the Zika virus were reported between February 2016 and January 2017 in Ahmedabad, the World Health Organization(WHO) confirmed in its disease outbreak bulletin[8] . It said the Centre confirmed the three cases, in two pregnant women and in an elderly man, on May 15, 2017.

The WHO bulletin said the first case was reported during a disease surveillance activity in Ahmedabad between February 10 and 16,2016. A 64-year old man with mild fever over eight days was detected with Zika virus. The second case was detected at BJMC where a 34-year-old woman delivered a baby on November 9,2016.

The third case was confirmed during an antenatal clinic (ANC) surveillance between January 6 and 12,2017 where a total of 111 blood samples were collected at BJMC. One sample from a 22-year-old woman in her 37th week of pregnancy was tested positive for Zika.

Discussion

Virology and Pathogenesis

Zika virus is a positive-sense single-stranded RNA virus in the family *Flaviviridae*, which includes several other mosquitoborne viruses of clinical importance (e.g., DENV, WNV, and yellow fever virus [YFV]) [9]. Its closest relative is Spondweni virus, the only other member of its clade [*9*]. The Zika virus genome contains 10,794 nt encoding 3,419 aa [*10*]. Like other flaviviruses, Zika virus is composed of 2 noncoding regions (5′ and 3′) that flank an open reading frame[10], which encodes a polyprotein cleaved into the capsid, precursor of membrane, envelope, and 7 nonstructural proteins[10].

Phylogenetic analysis shows that Zika virus can be classified into distinct African and Asian lineages; both emerged from East Africa during the late 1800s or early 1900s[11]. The Asian lineage originated during the virus's migration from Africa to Southeast Asia, where it was first detected in Malaysia. From there, Zika virus spread to the Pacific Islands, separately to Yap and French Polynesia, and then to New Caledonia, Cook Islands, Easter Island, and the Americas [11].

A study of Zika virus's molecular evolution, based on viral strains collected from 4 countries in West Africa during 1947–2007, identified several sites within the Zika viral genome that were under strong negative selection pressure. This finding suggests frequent purging of deleterious polymorphisms in functionally important genes and the possibility of recombination, which occurs rarely among flaviviruses[12]. The implications of this finding require further evaluation with respect to viral spread, zoonotic maintenance, and epidemiologic potential.

After mosquito inoculation of a human host, cellular entry likely resembles that of other flaviviruses, whereby the virus enters skin cells through cellular receptors, enabling migration to the lymph nodes and bloodstream. Few studies have investigated the pathogenesis of Zika virus infection. One study showed that human skin fibroblasts, keratinocytes, and immature dendritic cells allow entry of Zika virus[13]. Several entry and adhesion factors (e.g., AXL receptor tyrosine kinase) facilitate infection, and cellular autophagy, needed for flaviviral replication, enhances Zika virus replication in skin fibroblasts[13]. After cellular entry, flaviviruses typically replicate within endoplasmic reticulum-derived vesicles. However, Zika virus antigens were found exclusively in the nuclei of infected cells; this finding suggests a location for replication that differs from that of other flaviviruses and merits further investigation[14].

Transmission

Zika virus, like other flaviviruses, is transmitted by mosquitoes, primarily spread by the female *Aedes aegypti*[15] mosquito, which is active mostly in the daytime. The virus has also been isolated from a number of arboreal mosquito species in the *Aedes* genus, such as *A. africanus*, *A. apicoargenteus*, *A. furcifer*, *A. hensilli*, *A. luteocephalus* and *A. vittatus*.

Other nonvector modes of Zika virus transmission include congenital[16], perinatal[17], and sexual[18], blood transfusion[19] and animal bite[20].

Clinical symptoms

In humans, the incubation period from mosquito bite to symptom onset is ≈3–12 days. Infection is likely asymptomatic in ≈80% of cases[21]. All ages are susceptible (4 days–76 years), with a slight preponderance in females . When symptoms occur, they are typically mild, self-limiting, and nonspecific, similarity to other arbovirus infections (e.g., DENV and chikungunya virus [CHIKV]) may confound the diagnosis[22]. Commonly reported symptoms include rash, fever, arthralgia, myalgia, fatigue, headache, and conjunctivitis). Rash, a prominent feature, is maculopapular and pruritic in most cases; it begins proximally and spreads to the extremities with spontaneous resolution within 1–4 days of onset. Fever is typically low grade (37.4°c –38.0°c)[23].symptoms resolve within 2 weeks; rarely they may take longer time.

Infection during pregnancy causes microcephaly and other brain malformations in some babies.[24] infection in adults has been linked to guillain–barré syndrome (GBS).[25]

Diagnosis

Information on laboratory findings for Zika virus infection is limited. Complete blood count is often normal; even if blood count is abnormal, changes may be nonspecific (e.g., mild lymphopenia, mild neutropenia, mild-to-moderate thrombocytopenia)[26]. Mild elevations in inflammatory markers (C-reactive protein, fibrinogen, and ferritin), serum lactate dehydrogenase, or liver enzymes have been described[27]. These findings are observed in many other viral infections, including the co-circulating viruses DENV and CHIKV, so none of these laboratory alterations reliably distinguish among these infections.

Because of clinical overlap with other arboviruses, diagnosis relies on laboratory testing. Evaluation for Zika virus, CHIKV, and DENV should be undertaken concurrently for all patients who have acute fever, rash, myalgia, or arthralgia after recent (previous 2 weeks) travel to an area of ongoing Zika virus transmission[28].

Molecular amplification (e.g., RT-PCR) on serum samples remains the most specific diagnostic approach and is the preferred testing method for Zika virus during the acute phase of illness (<7 days from symptom onset)[28]. In contrast, serologic testing is not recommended during the acute phase, when Zika virus IgM may be undetectable . However, molecular testing must be performed during the viremic period . Several case reports of negative RT-PCR results but positive IgM results for patients whose samples were tested at ≥5 days after symptom onset indicate a possible viremic period as brief as 5 days[29]. Consequently, testing algorithms are based on sampling relative to symptom onset, and serologic testing should be considered if samples are negative for Zika virus by RT-PCR[28].

Serologic testing has limitations. Zika virus IgM and IgG are notoriously cross-reactive with those against other flaviviruses (particularly DENV), limiting specificity[30]. Therefore, positive serologic test results should be confirmed with testing that uses an alternative platform such as a seroneutralization assay (e.g., plaque-reduction neutralization test) . However, flaviviral cross-reactivity can also pose problems in confirmatory assays, especially for patients immunized (e.g., against YFV or Japanese encephalitis virus) or infected with another flavivirus (e.g., WNV or St. Louis encephalitis virus); presence of antibodies confounds diagnosis[28].

Although diagnostic testing is performed primarily on serum or cerebrospinal fluid, the diagnostic utility of other specimen types (e.g., urine, saliva, amniotic fluid, and tissue) is being evaluated[28]. Urine and saliva may offer alternatives, particularly when blood collection is difficult (e.g., in children or remote locations). Viruria may persist longer than viremia. One study reported that Zika virus RNA was detected in urine up to 20 days after viremia had become undetectable[31]; therefore, RT-PCR testing of urine should be considered when Zika virus is clinically suspected, despite negative serum testing . Similarly,

RT-PCR conducted with saliva has been shown to increase the detection rate during the acute phase of infection but does not extend the window of detection of Zika virus RNA; consequently, blood remains the preferred sample[32] .

Zika testing in pregnant women

CDC issued a Health Alert Notice (HAN) to share emerging evidence about interpreting Zika IgM antibody test results of pregnant women who may have been exposed to Zika virus, particularly women who live in or frequently travel to areas with a CDC Zika travel notice [33].

This HAN has specific recommendations not currently a part of the existing laboratory guidance, which should be considered for these women:

1. that nucleic acid testing is considered at least once per trimester unless a previous test has been positive, and on amniocentesis specimens, if amniocentesis is performed for other reasons.
2. IgM testing may be considered as part of pre-conception counselling.

Who to Test

All pregnant women in the United States and US territories should be assessed for possible Zika virus exposure at each prenatal care visit. Possible exposure to Zika virus that warrants testing includes

- Travel to or residence in an area with risk of Zika, or
- Sex (vaginal, anal, and oral sex) without a condom, or sharing sex toys with a person who traveled to or lives in an area with risk of Zika.

Laboratory evidence of a confirmed recent Zika virus infection includes

1. Detection of Zika virus or Zika virus RNA or antigen in any body fluid or tissue specimen; or
2. Positive or equivocal Zika virus or dengue virus IgM test on serum or cerebrospinal fluid (CSF) with a positive titer for Zika virus (≥10) from plaque reduction neutralization testing (PRNT) together with negative PRNT titer (i.e., <10) for dengue virus.

Testing Symptomatic Pregnant Women

Pregnant women who report signs or symptoms consistent with Zika virus disease (acute onset of fever, rash, arthralgia, conjunctivitis) should be tested for Zika virus infection. The testing recommendations for symptomatic pregnant women are the same regardless of the circumstances of possible exposure; however, the type of testing recommended varies depending on the time of evaluation relative to symptom onset.

Symptomatic pregnant women who seek care <2 weeks after symptom onset should receive testing of serum and urine by RNA nucleic acid testing (NAT; e.g. rt-PCR). A positive RNA NAT result confirms the diagnosis of recent maternal Zika virus infection. Symptomatic pregnant women with negative RNA NAT results should receive both Zika virus IgM and dengue virus IgM antibody testing. If Zika virus RNA NAT testing is requested from laboratories that do not have IgM antibody testing capacity or a process to forward specimens to another testing laboratory, storing of additional serum samples is recommended for IgM antibody testing in the event of a negative RNA NAT result. If either the Zika virus or dengue virus IgM antibody test yields positive or equivocal results, PRNT should be performed on the same IgM-tested sample or a subsequently collected sample to rule out false-positive results.

Symptomatic pregnant women who seek care 2–12 weeks after symptom onset should first receive Zika virus and dengue virus IgM antibody testing. If the Zika virus IgM antibody testing yields positive or equivocal results, reflex RNA NAT testing should be automatically performed on the same serum sample to determine whether Zika virus RNA is present. A positive RNA NAT result confirms the diagnosis of recent maternal Zika virus infection. However, if the RNA NAT result is negative, a positive or equivocal Zika virus IgM antibody test result should be followed by PRNT. Positive or equivocal dengue IgM antibody test results with a negative Zika virus IgM antibody test result should also be confirmed by PRNT.

Testing Asymptomatic Pregnant Women

Testing recommendations for asymptomatic pregnant women with possible Zika virus exposure differ based on the circumstances of possible exposure (i.e., ongoing versus limited exposure) and the elapsed interval since the last possible Zika virus exposure.

Asymptomatic pregnant women living in areas without Zika who are evaluated <2 weeks after possible Zika virus exposure should be offered serum and urine RNA NAT testing. A positive RNA NAT result confirms the diagnosis of recent maternal Zika virus infection. However, because viral RNA in serum and urine declines over time and depends on multiple factors, asymptomatic pregnant women with a negative RNA NAT result require additional testing to exclude infection. These women should return 2–12 weeks after possible Zika virus exposure for Zika virus IgM antibody testing. A positive or equivocal IgM antibody test result should be confirmed by PRNT.

Asymptomatic pregnant women living in an area without Zika, who seek care 2–12 weeks after possible Zika virus exposure should be offered Zika virus IgM antibody testing. If the Zika virus IgM antibody test yields positive or equivocal results, reflex RNA NAT testing should be performed on the same sample. If the RNA NAT result is negative, PRNT should be performed.

Asymptomatic pregnant women who have an ongoing risk for Zika virus exposure (i.e., residence in or frequent travel to an area with risk of Zika) should receive IgM antibody testing as part of routine obstetric care during the first and second trimesters. Reflex RNA NAT testing is recommended for women who have a positive or equivocal Zika virus IgM antibody test results because RNA NAT testing provides the potential for a definitive diagnosis of Zika virus infection. Negative RNA NAT results after a positive or equivocal Zika virus IgM antibody test result should be followed by PRNT. The decision to implement testing of asymptomatic pregnant women with ongoing risk for Zika virus exposure should be made by local health officials based on information about levels of Zika virus transmission and laboratory capacity.

Management and Prevention

No specific treatment or vaccine is available for Zika virus infection. Management is supportive and includes rest, fluids, antipyretics, and analgesics.

Aspirin and other nonsteroidal antiinflammatory drugs should be avoided until dengue is excluded because of the risk for hemorrhage among dengue patients.

Prevention of mosquito bites, including individual protection (e.g., long pants, light-colored clothing, insect repellants, bed nets), particularly during known *Ae. aegypti* peak biting times (early morning and late afternoon). Community-level strategies target mosquito breeding through elimination of potential egg-laying sites (e.g., potted plant saucers, water storage units, used tires) by drying wet environments or using insecticide treatment .

Conclusion

Zika virus has the propensity to infect large numbers of persons with severe consequences in some cases. Signs and symptoms mimic other flavivirus infections. Clinical diagnosis is difficult, molecular analysis using RT-PCR and serology are investigations of choice. NO specific treatment and vaccination is available. Prevention of the disease by targetting mosquito breeding through elimination of potential egg-laying sites (e.g., potted plant saucers, water storage units, used tires) by drying wet environments or using insecticide treatment.

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