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Zika virus: A review of literature

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ABSTRACT

Zika virus (ZIKV) has two lineages: African and Asian. Mosquito-borne flaviviruses are thought to replicate initially in dendritic cells and then spread to lymph nodes and the blood stream. Risk for infection through blood transfusion, sexual practices and perinatal transmission exists. The possible routes of perinatal transmission are during delivery, breastfeeding and by close contact between the mother and her newborn. Also, muco-cutaneous exposures to the virus by infected blood or monkey bite, organ transplantation or hemodialysis are the other routes of ZIKV transmission. There are two types of ZIKV infection; Zika fever and congenital infection. Clinical presentation of Zika fever varies from asymptomatic infections to a self-limiting febrile disease with low grade fever, conjunctivitis, maculopapular rash, headache, retro-orbital pain and arthritis/arthralgia with periarticular edema, myalgia, vertigo, vomiting and asthenia. This clinical feature could be mistaken for dengue or chikungunya fevers. Microcephaly is the most important and frequently reported clinical picture of suspected congenital Zika syndrome. Laboratory tests are needed for diagnosis of ZIKV infection, because there is no known pathognomonic clinical, biochemical or radiological features. RT-PCR is the most well-liked assay. Serum samples are tested by immunoglobulin G ELISA with ZIKV antigen. Samples are also tested by immunoglobulin M ELISA. There is no certified vaccine or therapeutic medication. In asymptomatic or uncomplicated patients, treatment is not necessary.

1. Introduction

Zika virus (ZIKV) is an arbovirus of the family Flaviviridae [1,2]. There are some other mosquito-borne flaviviruses which are important as public health issues including yellow fever, dengue, St. Louis encephalitis, West Nile and Japanese encephalitis viruses [3,4].

ZIKV has two families: African and Asian. In 2007, an epidemic was generated by the Asian family of ZIKV on Yap Island, Micronesia; it then broaden to French Polynesia and other regions of the South Pacific and led to extensive epidemics in 2013 and 2014; following this ZIKV came in the Americas in 2015, causing an estimated 1.5 million cases in Brazil in 2015 [5]. A new report of an association between ZIKV infection and an epidemic of microcephaly among Brazilian neonates attracted universal attention. ZIKV spreads fast from Africa and Asia to the Americas and Europe and the "congenital Zika syndrome" incidence has caused the World Health Organization (WHO) to notify the ZIKV epidemic as a public health crisis of the world at the beginning of February 2016 [6].

At first ZIKV infection was reported in Uganda in 1947 and sporadic cases were reported from 1960s in Asia and Africa [1,7–9]. After 2 years, several ZIKV isolates were obtained from *Aedes* spp. in Africa (*Aedes africanus*) and Malaysia [*Aedes aegypti* (*Ae. aegypti*)], involving these species as likely epidemic or enzootic vectors. Several ZIKV human isolates were also obtained in the 1960s and 1970s from East and West Africa. Additional serologic studies in the 1950s and 1960s detected ZIKV infections among humans in Egypt, Nigeria, Uganda, India, Malaysia, Indonesia, Pakistan, Thailand, North Vietnam and Philippines. Such data propose

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probable spread of ZIKV from Africa to Southeast Asia, west and north of the Wallace Line [10,11].

In May 2015, first patients with ZIKV infection were reported in Brazil and afterward in Colombia. Co-infection with dengue (DENV), chikungunya and ZIKV was reported in the same patients [12].

However, the clinical picture of ZIKV infection has been poorly described to date, since it causes a benign, self-limiting illness in most people; therefore, ZIKV infection has possibly been underreported in the endemic places [13–15].

In this article, we review the available literatures that may benefit clinicians to obtain necessary information regarding ZIKV infection.

2. Epidemiology

At the earliest during a study on yellow fever virus, ZIKV was isolated from the blood of a febrile sentinel Rhesus monkey in Zika jungle of Uganda in 1947. In 1948, ZIKV was isolated from *Aedes africanus* mosquitoes indicating that the virus might be mosquito-borne [4].

Zika virus has been quickly emerging in the western hemisphere over the past few months. It was first detected in Brazil, in the northeast and was subsequently recognized in other states and several South American countries including Colombia, Ecuador, Suriname, Venezuela, French Guyana and Paraguay. Transmission has been known in Central America (Panama, El Salvador, Honduras and Guatemala), the Caribbean (Martinique, Puerto Rico, Dominican Republic and Haiti) and Mexico. Transmission also occurred in travelers returning from the infected regions to non-endemic countries including United States, Canada, Japan and Western Europe. Since January 2016, a sum of 20 countries in the Americas has reported ZIKV infections [16].

Several *Aedes* species have been reported to be probable vectors of ZIKV including *Aedes hensilli* in Yap, *Ae. aegypti* and *Aedes polynesiensis* in French Polynesia. *Ae. aegypti* and *Aedes albopictus* are present in much of the Americas including many parts of the Southeastern and South Central United States as well as Hawaii [16].

In early 2015, an outbreak of ZIKV occurred in the state of Rio Grande do Norte, Brazil. Results of analysis revealed a high likeness of the sequences with Asian lineage. One theory regarding the introduction of ZIKV in Brazil is the arrival of the new emergent virus in 2014, during FIFA World Cup. In March 2015, another outbreak of ZIKV was occurred in the state of Bahia. The results of investigation on this outbreak showed that the obtained ZIKV sequences belonged to the Asian lineage with 99% identity with a sequence from a ZIKV isolate from French Polynesia and extend to other Pacific Islands. Since no endemic ZIKV endangered any of the Pacific countries during the FIFA World Cup, it has been hypothesized that the virus invaded Brazil through another occurrence that was held in Rio de Janeiro in August 2014, the “Va'a World Sprint Championship canoe race” where countries including French Polynesia, New Caledonia, Cook Islands and Easter Islands attended [17,18].

3. Virology

ZIKV is an approximately 11 kb positive-sense RNA virus that belongs to the genus *Flavivirus* in the family Flaviviridae [4,16]. Virions of ZIKV are 40–60 nm in diameter, spherical in shape and have a lipid envelope. The genome of ZIKA is a single-stranded RNA which has 10 794 nucleotides encoding 3 419 amino acids and contains two flanking untranslated regions (3′ and 5′ untranslated regions) and a single long open reading frame encoding a polyprotein that is infolded in capsid, precursor of membrane, envelope (E) and 7 non-structural (NS) proteins (50-C-prM-ENS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-30) [3,16,19]. The genomic RNA has a single long open reading frame flanked by 5′- and 3′-terminal non-coding regions that shape specific secondary structures necessary for genome replication and translation [16,19].

A key component on the surface of the virus is E protein that plays a role in the receptor binding and membrane fusion. The domain III of E protein includes a group of epitopes which are targets in neutralizing antibodies, serological tests and vaccines. Mosquito vectors adaptation and easy transmission of virus may be related to loss of N154 glycosylation site in the E protein. In addition, NS1 codon usage modification to human housekeeping genes that could make viral replication easier and increase viral titers may be related to the new spread of the Asian lineage of ZIKV to the Americas and Oceania [4].

4. Pathogenesis

Pathogenesis of ZIKV is almost unknown; however, it is found that mosquito-borne flaviviruses initially replicate in dendritic cells close to the inoculation site and then spread to lymph nodes and the blood. Although flaviviral replication is found to occur in cellular cytoplasm, studies suggest that ZIKV antigens can be found in nucleus of the infected cells. Moreover, infectious ZIKV has been detected in human blood before the beginning of symptoms [14].

After the replication, ZIKV may distribute from the lymphatics and blood stream to infect other organs of the body such as myocardium, central nervous system, skeletal muscles and to the fetus. The virus replication in astroglial cells and neurons in the brain of infected suckling mice result in neuronal degeneration, cellular infiltration and alleviation in the brain. Furthermore, the evidence of inflammation is found in myocardium and skeletal muscles in the infected mice. The neurotropism and tenacity of ZIKV may explain neurological complications such as microcephaly in congenital ZIKV infection [4].

5. Transmission

Rhesus monkeys can be the source in natural habitats of human infections through the bite of *Ae. aegypti* and *Aedes albopictus* in infected monkeys and subsequent transmission to vulnerable human hosts [20,21]. *Aedes* mosquitoes are found to be the most substantial vectors for ZIKV transmission; however, some *Anopheles*, *Culex*, *Eretmapodites* and *Mansonia* species have also been suggested as vectors. They bite both in house and in the open air and mostly during daytime [4,22]. It appears that viremia can start up to 10 days before onset of symptoms [23,24].

ZIKV is most likely maintained in a sylvatic cycle that includes non-human primates and mosquitoes with cyclic epizootics among monkeys in Uganda. Another emerging facet of the zoonosis has been the probable transmission through bites of monkeys and other non-human primates. In the sylvatic transmission cycle, humans possibly serve as incidental hosts; however, in areas without non-human primates, humans probably serve as primary intensification hosts [3,21].

Risk for infection through blood transfusion [15,25], sexual contact [17,26] and perinatal transmission [15] exists. The likely routes of perinatal transmission are transplacental during delivery, breastfeeding and by close contact between the mother and her baby through saliva and other body fluids exchange [20,21,23,27,28]. Sexual transmission of ZIKV seems to be highly probable, mainly in patients who have blood in semen. The sexual transmission of ZIKV to the female partner may infect the existing fetus. Other supposed routes of transmission are mucocutaneous contact to the virus in infected blood or via monkey bite, hemodialysis or transplantation. ZIKV infections have been documented through laboratory exposure. It is unidentified whether ZIKV can be spread by respiratory droplets [4,21,29,30].

Occurrence in birds and possible transmission from avian species to humans through insect intermediates has not been studied [7,23], although antibodies have been detected in several animal species [3].

6. Clinical presentations and differential diagnosis

Up to 80% of ZIKV infections may be asymptomatic. Patients with compromised immunity can be more vulnerable to develop severe disease if infected with ZIKV [5]. Symptoms expand after a bite by a Zika-infected mosquito with an incubation period of 2–14 days. ZIKV infection has two types including Zika fever and congenital infection [4].

Clinical presentations of Zika fever vary from asymptomatic infections to a self-limiting febrile sickness, presenting as a "dengue-like" syndrome with low fever, bilateral conjunctivitis, maculopapular rash, headache, retro-orbital pain and arthritis/arthralgia with edema of the tiny joints of hands and feet, myalgia, vertigo and asthenia [1,4,10,17,30]. Occasionally, sore throat, cough and loose bowels are reported [31]. Conjunctivitis in Zika fever is non-purulent and bilateral and the rash is reported to be erythematous and generalized that spreads from the face to the both limbs. There are some important systemic symptoms that are presented by high fever, chills, rigors, sore throat, hypotension, cervical, submandibular, axillary and/or inguinal lymphadenopathies. In addition, digestive symptoms may also be present including nausea, vomiting, diarrhea, constipation, abdominal pain and aphthous ulcers. Patients with genitourinary symptoms including hematuria, dysuria, perineal pain and hematospermia often have measurable virus particles in urine and/or semen [4]. This clinical feature can be wrong for dengue or chikungunya fevers [3]. Some presentations may distinguish Zika fever from chikungunya and dengue fever including more eminent edema of the extremities, less severe headache and milder thrombocytopenia reported in the former. Additionally despite dengue fever, hemorrhagic complications are not reported in Zika fever. Moreover, arthralgia in Zika fever is not as much as that of chikungunya fever [4,13,17]. These presentations are not pathognomonic and laboratory tests are required to exclude other causes of febrile diseases. As a matter of fact, Zika can be misdiagnosed during the acute stage because of nonspecific signs and symptoms. However, neurologic complications including Guillain-Barré syndrome (GBS) have been reported [4,13].

The rashes may be pruritic and usually resolves within the first week, but may remain for two weeks. It is important to exclude other infections such as chikungunya, DENV, measles virus, rubella virus, parvovirus B19, enterovirus, adenovirus and rickettsial infection. Duration of arthralgia is 3–5 days but, in some patients, arthralgia may be persistent or recurrent for more than 30 days after symptom initiation. Lymphadenopathies may last for 14 days after symptom onset and other infectious diseases including mononucleosis-like syndrome, toxoplasmosis and *Streptococcus pyogenes* should be came in mind [4,32,33].

6.1. Congenital Zika syndrome

Microcephaly is the most common clinical presentation of congenital Zika syndrome. Neonates and fetuses with suspected ZIKV infection are also found to have some other malformations including low birth weight, anasarca, unnecessary scalp skin, polyhydramnios and arthrogryposis. Neurological complications may also exist encompassing polymalformative syndromes, cerebral lesions, brainstem dysfunction and absence of swallowing. Ophthalmological deficiencies include cataract, intraocular calcifications, asymmetrical eye sizes, optic nerve hypoplasia, macular atrophy, iris coloboma and lens subluxation. Other features such as hepatosplenomegaly, rash and chorioretinitis have not been reported [4]. It is important to mention that there are no large studies to present a causal relation between ZIKV in the fetus and the congenital anomalies after exclusion of other infections. Hence, exclusion of the "TORCH" (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus-2 or neonatal herpes simplex) infections is needed for the diagnosis of congenital Zika syndrome. As a matter of fact, there are numerous etiological agents related to microcephaly including genetic disorders, drug intoxication of the pregnant woman (*i.e.* use of alcohol, cocaine or antiepileptic drugs), maternal malnutrition and transplacental infections [4,23,34–38].

The risk of microcephaly in the neonates appears to be mostly occurred in the first trimester of pregnancy [23]. Heart and muscle abnormalities should also be excluded. It is likely that intrauterine ZIKV infections that happen at a later time of the pregnancy may have different presentations, either with less severe abnormalities such as deafness, eye lesions and mental retardation [4].

6.2. Complications

Heart complications and immune thrombocytopenic purpura have also been found in a few cases. In Eastern Nigeria, jaundice was reported in patients with serological or virological evidence of ZIKV infection that also had malaria, microfilaremia and sickle cell anemia. Furthermore, the incidence rate of GBS cases was 20-fold higher than expected at the epidemic time of ZIKV [4,15,24,33].

Other abnormalities related to ZIKV infection include encephalitis, meningoencephalitis, myelitis, paresthesia, vertigo, facial paralysis, photophobia and hypertensive iridocyclitis and auditory features [4]. The findings of a relation between ZIKV infection and hydrops fetalis propose that the virus may make damage to tissues in addition to the fetal central nervous system. New studies found that histopathologic findings and detection of ZIKV in newborns and fetuses with microcephaly were restricted to the brain and placenta [39].

No death, hospitalization or hemorrhagic complication was observed during the epidemic on Yap Island; however, in Brazil, three deaths have been observed in relation with ZIKV. Newly in Colombia, death of an adolescent with sickle cell anemia has been reported [4,34].

7. Diagnosis

Laboratory approval is necessary for diagnosis of Zika infection considering that there is no pathognomonic presentation that differentiates Zika fever from other infections as well as congenital ZIKV infection from other etiologies of congenital abnormalities [4].

There are two types of diagnosis for ZIKV. The first type includes the detection of the virus or viral particles. RT-PCR, immunoassay and virus isolation have been invented to identify ZIKV RNA, viral proteins and live virus, respectively. RT-PCR is the most well-liked assay because of its high sensitivity and specificity, while virus isolation is the gold standard but requires more laboratory facilities for cell culture. Most importantly, viral culture is not usually performed. The second type of diagnosis is based on the detection of antibodies [5,30]. Serums samples are examined by immunoglobulin G ELISA with ZIKV antigen as well as the samples are tested by immunoglobulin M (IgM) ELISA with the viral antigens of Zika virus, DENV, yellow fever virus, Japanese encephalitis virus and Murray Valley encephalitis virus [11]. Furthermore, plaque reduction neutralization assay has improved specificity more than immunoassays, but may still earn cross-reactive results in secondary flavivirus infections [14]. Although serologic testing can identify the virus, dengue may make false positive results; therefore, positive results must be confirmed by the plaque reduction neutralization assay [13,16].

The cross-reactivity of antibodies between flaviviruses confines apply of serology [29]. Cross-reactivity is more often renowned with dengue virus than with yellow fever, Japanese encephalitis, Murray Valley encephalitis or West Nile viruses. Cases with primary ZIKV infection and precedent DENV infection are more likely to produce higher titer of IgM or neutralizing antibodies in opposition to ZIKV than against DENV. IgM may be identified on as early as day three of symptom beginning and may continue for over two months. IgM antibodies to dengue virus usually do not continue longer than 90 days. Neutralizing antibodies recognized by the plaque reduction neutralization test have more specificity than IgM detection by ELISA; however, the results may be indeterminate in patients who have prior vaccination history in opposition to other flaviviruses [4,5,7,14].

Quick and precise diagnosis of ZIKV infection has been earned by the application of RT-PCR via primers that target the E or NS5 gene [4,7]. RT-PCR may let simultaneous detection of more than fifty different flaviviruses. Urine and semen samples may have higher viral loads than serum samples and may be tirelessly positive for more than 30 and 62 days after symptom onset, respectively. As dating of symptoms beginning is not easy during Zika fever, using a mixture of samples including blood, saliva, urine, semen and nasopharyngeal is recommended [4,7,13,19,30].

Laboratory profiles are often normal. Although, some patients may have some hematological changes including leukopenia, neutropenia, lymphopenia, monocytosis, thrombocytopenia and high serum levels of lactate dehydrogenase, aspartate aminotransferase, fibrinogen, g-glutamyl transferase, ferritin, C-reactive protein and erythrocyte sedimentation rate [4].

Indications for testing during acute ZIKV disease should be supposed in individuals who: (a) traveled to or resided in an affected area within the past two weeks; (b) have 2 of the advents including fever, rash, conjunctivitis or arthralgia.

For probable acute ZIKV disease: (a) if symptoms have been in attendance for less than seven days, test serum and if obtained for other reasons, cerebrospinal fluid for ZIKV RNA by RT-PCR; (b) if ZIKV RNA is not identified and symptoms have been present for equal or more than four days, check serum for ZIKV IgM and neutralizing antibodies and dengue virus IgM and neutralizing antibodies.

Acute ZIKV disease should also be supposed in an infant during the first two weeks of living: (a) whose mother traveled to or resided in an affected area within two weeks of delivery; (b) who has equal or more than two of the advents including fever, rash, conjunctivitis or arthralgia.

Indications for testing regarding congenital infection include: (a) an infant with microcephaly or intracranial calcifications born to a woman who traveled to or resided in a place with ZIKV transmission as she was pregnant or (b) an infant born to a mother with a positive test for ZIKV infection.

For all infants with probable congenital ZIKV infection, do the following: (a) physical examination including size of occipito-frontal circumference, length, weight and evaluation of gestational age; (b) assessment for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly and rash or other skin lesions; (c) cranial ultrasound; (d) assessment of hearing by otoacoustic emissions or auditory brainstem response testing, either before discharge from the hospital or within one month after delivery; (e) examination of the retina, either before discharge from the hospital or within one month after labor.

Other important evaluations for infants with microcephaly include the following: (a) consultation with a pediatric neurologist to decide other evaluation including ultrasound, computerized tomography scan, and magnetic resonance imaging; (b) testing for other infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus infections.

For infants, RT-PCR assay should be conducted for ZIKV RNA and ZIKV and dengue virus IgM and neutralizing antibodies on serum composed from the umbilical cord or straight from infant within two days of delivery, if probable. It should be incorporated with histopathologic evaluation of the placenta and umbilical cord with ZIKV immunohistochemical staining and RT-PCR.

For all infants with likely congenital ZIKV, the most important recommended long-term follow-ups are: (a) conducting hearing screen at six months of age; (b) evaluating occipito-frontal circumference and developmental characteristics during the first year of living [34,36,37,40].

8. Treatment

There is no certified therapeutic or preventive medication available for ZIKV. Treatment is often not required for patients with asymptomatic or uncomplicated Zika fever [4,22,23].

Two strategies can be followed for ZIKV antiviral invention. The first is to re-target existing clinical medications which have been previously developed for other disease indications for ZIKV treatment. Some of the drugs did show antiviral activity in cell culture. The second strategy is to build up inhibitors of ZIKV. The experience gained from DENV drug invention can be applied to ZIKV; however, concern should be considered when extrapolating DENV antiviral experience to ZIKV, because the viruses are genetically separate and the biology of the two viruses can be very diverse. Therapeutic antibodies can also be applied for treatment of ZIKV. One challenge for the development of ZIKV antiviral is the high risk of adverse effects for pregnant women [5].

Treatment of Zika fever is supportive and includes acetaminophen for fever, headache or myalgia. Aspirin must be avoided because of the risks of bleeding in those with thrombocytopenia [16] and increasing Reye's syndrome in children [4]. Non steroidal anti-inflammatory drugs are also not suggested because of the increased risk of hemorrhagic syndrome [22]. Enough rehydration for fluid loss should be applied. It is necessary to diagnose neurological complications especially GBS for early prescription of intravenous immunoglobulins [4].

Based on earlier studies, some of the drugs that target hepatitis C can have some special effects on ZIKV. Anti-malarial hydroxychloroquine is an autophagy inhibitor and *in vitro* testing has shown inhibition of dengue virus. Moreover, amodiaquine works via blockage of autophagy and inhibits Zika virus pathogenicity. Immunotherapeutic strategies may propose hope for reducing clinical complications from ZIKV including GBS. Additionally, prophylactic and therapeutic use of cross-reactive neutralizing monoclonal antibodies for flavivirus infections has been shown to be influential in animals [23].

9. Prevention

There is no vaccine available for ZIKV. At present, there are approved vaccines for four flavivirus diseases. Both inactivated and live attenuated virus vaccines can be applied to ZIKV. Other vaccine approaches include subunit, DNA and viral vector vaccine platforms, all of which enclose or express ZIKV structural proteins [4,5,16].

Flaviviruses are inactivated by temperatures above 56 °C for at least 30 min, UV light and gamma radiation. The viruses are known to be vulnerable to disinfectants such as 1% sodium hypochlorite, 2% glutaraldehyde, 70% ethanol, 3%–6% hydrogen peroxide and 3%–8% formaldehyde. ZIKV is inactivated by potassium permanganate, and ether [14,19].

Inhabitants in or travelers to affected places should remain inside with air conditioning, window and door screens if plausible, wear long sleeves, use permethrin smeared clothes and equipment and use insect repellents when outside. Insect repellents encompassing *N*,*N*-diethyl-m-toluamide should be attached for children older than two months, pregnant and lactating women. For people coming back from affected areas to non affected places, it is important to use insect repellents for at least a further fourteen days [4]. Most importantly, World Health Organization has recommended that pregnant women should get safety measures to keep away from making contact with all potential vectors until the epidemic is over [16,17,36,37].

Regarding blood transfusion, testing of blood donors is suggested. When an outbreak happens, blood donation should be temporary discontinued. In non-endemic places, using pre-donation questionnaire is helpful to screen donors who recently traveled to affected areas and delay of blood donation from these donors until at least fourteen days after returning from affected places should be done. It is substantial to test donated organs of individuals who had history of travel to affected regions for ZIKV. Returned men travelers should persist to use condoms with pregnant sex partner all over the time of pregnancy [4].

Conflict of interest statement

We declare that we have no conflict of interest.

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